Daniel Pinto

Modifying Factors for Drug Prescription Behavior in Primary Care

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MODIFYING FACTORS FOR DRUG PRESCRIPTION BEHAVIOR IN PRIMARY CARE

FACTORES MODIFICADORES DO COMPORTAMENTO DE PRESCRIÇÃO DE MEDICAMENTOS EM CUIDADOS PRIMÁRIOS

DANIEL PINTO

Tese para obtenção do grau de Doutor em Medicina

na Especialidade em Investigação Clínica

na NOVA Medical School | Faculdade de Ciências Médicas

Setembro, 2017

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Orientadores: Professora Doutora Isabel Santos,

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To my family, with whom I share none of the credit, but make everything possible

Underlying scientific work

This thesis uses content from the following studies:

Study 1: initial therapeutic choices for arterial hypertension in the Portuguese Sentinel Practice network.

Co-authors: Ana Paula Rodrigues (Department of Epidemiology, Dr. Ricardo Jorge National Institute of Health – Lisbon, Portugal); Baltazar Nunes (Department of Epidemiology, Dr. Ricardo Jorge National Institute of Health – Lisbon, Portugal)

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Study 2: Initial therapeutic choices for type 2 diabetes in the Portuguese Sentinel Practice Network

Co-authors: Ana Paula Rodrigues (Department of Epidemiology, Dr. Ricardo Jorge National Institute of Health – Lisbon, Portugal); Baltazar Nunes (Department of Epidemiology, Dr. Ricardo Jorge National Institute of Health – Lisbon, Portugal)

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Study 3: Effect of European Medicines Agency's restrictions on trimetazidine utilization in Portugal

Co-authors: Ana Silva (Infarmed Portuguese Medicines Authority – Lisbon, Portugal), Bruno Heleno (Group for Independent Academic Information, Nova Medical School | Faculdade de Ciências Médicas – Lisbon, Portugal), David Silvério Rodrigues (Group for Independent Academic Information, Nova Medical School | Faculdade de Ciências Médicas – Lisbon, Portugal), Isabel Santos (Group for Independent Academic Information, Nova Medical School | Faculdade de Ciências Médicas – Lisbon, Portugal), Pedro A Caetano

(formerly of Group for Independent Academic Information, Nova Medical School | Faculdade de Ciências Médicas – Lisbon, Portugal)

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Study 4: Effect of European Medicines Agency's Regulatory Measures on Nimesulide Utilization in Portugal

Co-authors: Ana Silva (Infarmed Portuguese Medicines Authority – Lisbon, Portugal), Bruno Heleno (Group for Independent Academic Information, Nova Medical School | Faculdade de Ciências Médicas – Lisbon, Portugal), David Silvério Rodrigues (Group for Independent Academic Information, Nova Medical School | Faculdade de Ciências Médicas – Lisbon, Portugal), Isabel Santos (Group for Independent Academic Information, Nova Medical School | Faculdade de Ciências Médicas – Lisbon, Portugal), Pedro A Caetano (Group for Independent Academic Information, Nova Medical School | Faculdade de Ciências Médicas – Lisbon, Portugal). António Faria-Vaz (Pharmacy and Therapeutics Committee, Lisbon Regional Health Administration) also participated in the early stages of the project, but did not meet authorship criteria for this manuscript.

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Study 5: An open cluster-randomized, 18-month trial to compare the effectiveness of educational outreach visits with usual guideline dissemination to improve family physician prescribing

Co-authors: Bruno Heleno (Group for Independent Academic Information, Nova Medical School | Faculdade de Ciências Médicas – Lisbon, Portugal), David S Rodrigues (Group for Independent Academic Information, Nova Medical School | Faculdade de Ciências Médicas – Lisbon, Portugal), Inês Gomes (Interdisciplinary Center fo Social Sciences, Faculdade de Ciências Sociais e Humanas – Lisbon, Portugal), Ana Luísa Papoila (Biostatistics Department, Nova Medical School | Faculdade de Ciências Médicas – Lisbon,

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List of abbreviations

ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blocker
ATC	Anatomical therapeutic chemical classification
CCB	Calcium channel blocker
CHMP	Committee for Medical Products for Human Use
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase-2
DDD	Defined daily dose
DPP-4	Dipeptidyl peptidase-4
EC	European Commission
EMA	European Medicines Agency
FP	Family physician
GLP1	Glucagon-like peptide-1
ICC	Intra-cluster correlation coefficient
ICPC	International Classification of Primary Care
INFARMED	Portuguese National Medicines Authority
ITS	Interrupted time series
NHS	National Health Service
NSAID	Non-steroidal anti-inflammatory drug
OECD	Organisation for Economic Co-operation and Development
PPI	Proton pump inhibitor
SD	Standard deviation
SPC	Summary of product characteristics
TEP	Trial to Assess the Effectiveness of Educational Outreach in Prescription Guidelines

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Preface

The preface is written somewhat informally, in a non-technical language. It is here to help the reader place this thesis in context. It is about me and how I got here. I didn't always follow a straight line, but I am pleased with the place where this journey led me.

The path to a PhD

Curiosity about the world and the way it works has always been present. I have a hard time accepting something without understanding it, questioning its assumptions and seeing its effects.

During my last year in medical school I had the opportunity to do a small research project during the family medicine rotation. The question was simple: do patients take their prescribed medicines? It arose when my tutor was renewing prescriptions for patients who had left a request at the clinic, but had not come to a face-to-face visit. Why did some have such long gaps in between prescription renewals? It was the first time I did something that felt like real research, not just an exercise to turn in and get approval in a class.

After that, questions kept coming up and the need to answer them grew. I was a family medicine resident by then. I had the support of my tutor and worked with other residents doing small research projects. However, at some point, I began to feel like an amateur. I had the will, but lacked knowledge about research methods and statistics, a larger team to criticize my ideas and funding to make projects happen.

One day my tutor asked me if I had ever considered doing a PhD. I wasn't expecting such a question. No, PhDs were for experienced and really good clinicians. I was just a resident! But he had planted a seed. A PhD wasn't an award for being a good clinician, it was a way to learn to be a better researcher. By then I had tasted research, amateurish as it may have been, and I liked it. Maybe it could become a greater part of what I did, even a part of my job. And I needed to learn more about how to become a better researcher, just like I was learning to become a better clinician with the residency program.

After a few months, the idea settled in: I was going to apply for a PhD, but only after I had finished my residency training in 2010.

Choosing a subject

Before enrolling in the PhD program, I needed a subject. I had an interest in the International Classification of Primary Care, but not a very good idea on how to build a thesis on the subject. Another area of affinity was evidence based medicine, namely rational use of medicines and tests. I was in contact with the head of the family medicine department at NOVA Medical School, Professor Isabel

Santos, and had discussed some ideas with her. An opportunity came when a new researcher joined the faculty at the pharmacology department - Professor Pedro Caetano. He had experience in epidemiological research abroad and was keen on improving care in Portugal. He had been in contact with a group from Harvard Medical School led by Jerry Avorn doing academic detailing (or educational outreach visits) in the United States. We talked and an idea started to develop into a project: to bring educational outreach visits to Portugal. We would try to demonstrate its feasibility and effectiveness, hoping to convince the Ministry of Health to implement this technique nationwide if we were successful. It was in one of my areas of interest, innovative and it could matter in improving the quality of healthcare being delivered. I had a subject and was ready to enroll in the PhD program.

Laying the foundation

To do educational outreach visits you need a subject and a message to communicate. Luckily, around that time, the Portuguese National Health Directorate was looking for academics to develop guidelines for primary care and other physicians. It was an opportunity we could not waste. This was not something that could be done by a single person, so we gathered a team and the family medicine and pharmacology departments of NOVA Medical School were commissioned to produce four guidelines on subjects chosen by the National Health Directorate: non-steroidal anti-inflammatory drugs (with a focus on COX-2 inhibitors), acid secretion modifiers (with a focus on proton pump inhibitors), antiplatelets (with a focus on clopidogrel) and antibiotics in pneumonia.

We began to work by the end of 2010. For the first three subjects, the American group had already done literature reviews and produced brochures and other materials for educational outreach. Instead of starting from scratch, we entered an agreement with them to adapt their materials. Adapting involved updating the literature review, understanding what made sense in the Portuguese health system, translating, and validating our work with focus groups composed of primary care clinicians. For pneumonia, we started in the previous step, conducting the literature review. We also had to consider differences in drug resistance patterns from were research had been conducted to what was documented in Portugal.

While we were working, the country was in turmoil. A financial crisis had struck, the Prime-Minister had resigned in March 2011 and in May the country signed a memorandum of understanding with European Financial Stabilization Mechanism, the European Financial Stability Facility, and the International Monetary Fund to a €78 billion financial assistance package. The memorandum of understanding had one very relevant item that would affect our work: "3.59. Establish clear rules for the prescription of drugs and the realization of complementary diagnostic exams (prescription guidelines for physicians) on the basis of international prescription guidelines." This brought about changes in the way the National

Health Directorate was producing guidelines. There would be many more groups making guidelines on other subjects and all had to follow a similar template. We had to change structure and formatting, guidelines would first be published as drafts for public comment, a reply to those comments had to be prepared and latter be sent for approval by an expert Committee. We became convinced that these changes would make guidelines less user friendly and would decrease their effectiveness. Instructions from the National Health Directorate changed often, prompting us to review much of the work that had been submitted before. Trying to reach a final version of each guideline would take over three years.

Getting funded

Producing guidelines was only about laying a foundation to do research and not the research project itself. The best way to prove the efficacy of an intervention is through a randomized controlled trial. But to conduct a randomized controlled trial you need money. Getting funded was one of the hardest parts of the job. In 2011 the Ministry of Health had a call for research projects in primary care. The available funding was relatively small and the call had been designed with less lengthy projects in mind. Yet, it was an opportunity and it gave us the change to prepare a protocol for the trial. We submitted and waited for a decision.

In 2012 we applied for a research grant from the Foundation for Science and Technology (the Portuguese national funding agency for science, research and technology). It would be a larger grant and allow for more time to finish the project. We made major improvements to the research protocol during this stage. We had collected pilot data, could accurately calculate a sample size, decided on the outcomes and on several other details, registered the trial and applied for a study seal from the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance. We had done so much work, the group decided to submit the protocol for publication. The grant decision came a few months later. Although our project was rated as excellent on all criteria, it was not chosen for funding due to budget limitations.

This was a major blow, as it would be impossible to complete the project without funding. A glimmer of hope arrived in December 2012, when we were informed that the Ministry of Health had decided to fund our project. We wouldn't get all the money we had applied to and we had little time to finish, but believed we could make it work with some adjustments and a lot of cost saving.

Sidetracked

Since enrolling in the PhD program, I had reduced my working ours as a clinician, but never stopped seeing patients. I didn't want to study something very distant from clinical practice, and what I saw with patients motivated me to pose research questions. In 2011 I received a letter from a drug company and the Por-

tuguese Medicines Authority. It was about the non-steroidal anti-inflammatory drug nimesulide; the European Medicines Agency had recommended several restrictions on its use due to safety concerns. I didn't prescribe the drug very often, so it was easy to stop. However, in the following weeks I noticed some of my patients still came to a visit telling me that had seen another doctor, usually in the hospital, and had been prescribed nimesulide. I wondered how effective were the recommendations from a regulatory authority on physicians actual practice and if primary care and hospital physicians reacted differently. I would need to gather data on nimesulide use over time, see if any change had happened and make sure it wasn't due to chance or other factors. This was something I could add to my thesis, as I would be observing the effects of an intervention on physician prescribing behavior. It wasn't an intervention I could control, like in the randomized controlled trial, but an intervention nonetheless.

As a family physician, patients often asked me to renew prescriptions that had been initiated by other physicians, at a hospital visit or in private practices. For some drugs, I was glad to do it, but not for others. Sometimes I would not agree with the prescription because I believed it was not the right treatment for that patient, but more often because I believed the drug had not demonstrated a good benefit-risk or benefit-cost profile. One of those drugs was trimetazidine and, when in 2012, recommendations for restricted used were made by the European Medicines Agency, I seized the opportunity to stop prescribing it. As with nimesulide, some of my patients kept asking me for it because another doctor had told them to keep taking it. I decided to study the effects of the recommendations for restricted trimetazidine use and include it in my thesis.

However, it isn't easy to change a drug being prescribed by another physician when you don't have a strong authoritative statement to back you up. More often than not, it comes down to the way different physicians interpret current medical knowledge and their personal values. I would sometimes prefer that a patient was being treated differently, but other physicians also treating them may hold a different opinion. This is normal and a problem only arises when the patient asks me to prescribe a drug that was decided by someone else and with which I do not agree. Many family physicians complain about this problem and feel it difficult to change the patient's treatment. They feel a part of their prescription is not their own direct responsibility. The prescribing behavior of family doctors was being changed by other physicians that shared their patients.

I considered this was a real problem, but I could not say how large it was. I then began to think of a way to measure it. Looking at newly diagnosed patients would be a more reliable way, as it would be difficult to gather from a database who first prescribed a drug, even with reliable individual patient data. The Sentinel Practice Network would be a good way to prospectively collect data. To measure prescriptions made by other physicians I would have to choose a chronic problem, so that

patients would come to their family doctor and share what had been prescribed by other physicians. Diabetes and hypertension were the obvious choices, as they were two of the major drivers of drug expenditures in Portugal.

Setbacks

A major hurdle that had to be tackled throughout the PhD's research projects was how to access prescribing data. The Portuguese National Health Service, being a single payer system with centralized records, was ideal for studying prescriptions of reimbursed drugs. However, not much research had been allowed with the Ministry of Health's databases. Getting through authorizations and bureaucracy was very time consuming. There were also validation issues, as the database structure is complex and sparsely documented, there are no dedicated researchers in the Ministry of Health and some of what we did had never been tried before. Often there were problems with the first data extraction attempts. Fortunately, these could be corrected, as the database did hold the necessary records.

The PhD led me and other members of the research team to learn new skills. This was both challenging and gratifying, as we were all eager to learn. None of us had ever done randomization by minimization, managed a randomized control trial or used time-series methods. We tried to cooperate with other research units in NOVA University, with people that had the needed research knowledge. However, for one reason or another, most of them did no go through. This caused delays, but did not prevent us from achieving our goals and the team is now empowered to do more in the future.

Putting it all together

As described above, the thesis was constructed around three research projects: a randomized controlled trial to test the effectiveness of educational outreach visits; two interrupted time-series observational studies to evaluate the effectiveness of regulatory measures on drug use; and two observational studies on how patients with diabetes and hypertension are first treated, highlighting differences between primary care clinicians and other physicians. Each study has been planned, conducted and reported both to stand individually and to be part of a larger view on the thesis' subject: understanding what influences prescription behavior with an emphasis in primary care.

Naturally, the thesis could not encompass all questions that still remain to be answered in this field. Instead, it gives context to the subject of influencing prescription behavior, addresses some of the unanswered questions and draws conclusions about what was found. To achieve this goal, the thesis is divided in six parts. Part one will discuss what is known about factors that influence prescription behavior and gaps in current knowledge. It also provides some context on the work done in the thesis, covering scientific aspects not intended for this preface. Part two out-

lines the aims and objectives for the thesis. Parts three to five present each of the studies done. They are grouped and ordered according the questions they try to answer. Part three begins with the two studies conducted in the Sentinel Practice Network, documenting how physicians behave when they have an opportunity to decide on a treatment and how physicians may influence each other when they share patients. Part four describes the influence of drug regulatory agencies when they interact with physicians, but also how other factors occurring at the same time may play a role. Part five describes how an educational outreach program could be implemented, the views or participants (both those receiving and those doing the visits) and their effectiveness in changing prescribing behaviors. Finally, part six draws global conclusions from the studies that were presented and highlights their implication for practice and future research.

Acknowledgments

A PhD is a degree that is conferred to a person, but getting there is by no means something you do alone. Many people have contributed to the work presented in this thesis and have helped me along the way. I would like to thank them all for their contribution.

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Teresa, for keeping me focused, being a patient listener, understanding, giving me strength and being an honest critic of my ideas and work.

My mother and father, who encourage me no matter what, stimulate me to be an independent thinker, and provide everything so that I can pursue my dreams.

Abstract

Background

Medical science can provide evidence on what high quality care should look like. However, there is a gap between research findings and routine clinical practice. Physicians do not always act like what the best scientific evidence would recommend, but aiming for high-quality, high-value care is important as it benefits patients. Clinical practice guidelines aim to assist clinicians in this task by providing critically appraised summaries of the best current medical knowledge and recommending how to proceed. However, often, clinicians will fail to follow guideline recommendations. Medical prescribing is not only determined by knowledge, competence, benefit-risk and cost-effectiveness. Other factors such as personal values, beliefs, attitudes and experiences, health services organization, the availability of information, patient characteristics and requests, peer interactions, marketing techniques, reciprocity, authority, social validation and personal relationships are also decisive. To some extent, primary care physicians may be influenced by specialists to prescribe drugs they would have otherwise not choose.

Many interventions have been studied with the purpose of improving clinical practice. Most interventions show small to moderate effects on prescription improvement. However, there is considerable heterogeneity in results, which probably reflects lack of standardization and the interference of setting specific factors. Two specific interventions are educational outreach visits, aimed at changing healthcare professionals' behavior by delivering educational content in face-to-face visits; and regulation authorities' risk minimization measures, meant to improve the benefit-risk balance of drugs after they have been approved.

The general aim of this thesis is to contribute to the understanding of how primary care physicians decide to prescribe drug treatments and how they can be influenced. Specific objectives are to describe how physicians initiate treatment in hypertension and type 2 diabetes and if there are differences between family physicians and other specialists; to assess the effect of regulatory actions taken by the European Medicines Agency to restrict the utilization of trimetazidine and nimesulide; and to determine the efficacy and cost-effectiveness of educational outreach visits to improve compliance with guideline recommendations.

Methods

The thesis contains seven research manuscripts, divided in three parts. The first two studies were cohort-nested cross-sectional studies done within the Portuguese Sentinel Practice Network. Family physicians notified incident cases of arterial hypertension and type 2 diabetes, reporting treatment, who made the initial prescription and if they had changed treatments initiated by other physicians.

The second group contains two interrupted time-series analysis of ambulatory pharmacy reimbursement records for the Portuguese National Health Service. Effects of the European Medicines Agency risk minimization measures on prescription of trimetazidine and nimesulide were measured. Regulatory actions were identified by searching the European Medicines Agency, Portuguese Medicines Authority and European Commission's websites. Confounding factors in the same period were also identified. Segmented regression models were built assessing the effects on dispensing of trimetazidine and nimesulide, both globally and for physicians in National Health Service primary care, National Health Service hospitals and other settings. For nimesulide, adverse drug reactions were also measured.

The third group contains a parallel, open, superiority, randomized trial directed to primary care physicians. Physicians were recruited in clusters of primary care practices and randomly allocated to receive educational outreach visits at their workplace or usual guideline dissemination. Primary outcomes were the proportion of cyclooxygenase-2 (COX-2) inhibitors prescribed in the anti-inflammatory (NSAID) class, and the proportion of omeprazole in the proton pump inhibitors class at 18 months post-intervention. Secondary outcomes were the proportion of COX-2 inhibitors within the NSAID class at one and six months; the proportion of omeprazole within the proton pump inhibitors class at one and six months; and the number of defined daily doses of clopidogrel prescribed per 1,000 registered patients at 1, 6 and 18 months. Prescription data was collected from the regional pharmacy claims database. Costs were also measured to perform a cost-benefit analysis. The trial was also subjected to a process evaluation by gathering data on recruitment of physicians and detailers, recording a post-visit questionnaire, conducting a focus group with detailers, interviewing participating physicians and send a questionnaire to physicians in the intervention arm.

Results

The studies on initial treatment for hypertension and diabetes showed that family physicians made the majority of diagnosis and there was very high compliance with guideline recommendations in both conditions. Angiotensin converting enzyme inhibitors were the most used drugs to initiate anti-hypertensive treatment and metformin was most used for type 2 diabetes. Some differences were observed between family physicians and other doctors, with the former prescribing less beta-blockers and loop diuretics in hypertension and less dipeptidyl peptidase-4 inhibitors and insulin in type 2 diabetes. In both cases, prescriptions initiated by other specialists were rarely altered by family physicians.

The studies on trimetazidine and nimesulide showed significant decreases in use of these drugs associated with complex interventions consisting of regulatory risk minimization measures and other concurrent factors. However, not all actions by regulatory authorities led to changes in drug use and concurrent factors such as

media coverage may have played an important role. Family physicians were more compliant with recommendations to restrict nimesulide use than hospital or private based physicians, while for trimetazidine they were less compliant (after adjusting for differences in global market share). There were no changes in clinical adverse events for nimesulide.

The randomized controlled trial of educational outreach visits was successfully implemented, visits occurred as planned, and were acceptable to participating physicians. Yet, the intervention was not effective in improving primary or secondary outcomes or reducing costs.

Conclusions

The two studies in the Portuguese Sentinel Practice Network showed that physicians mostly follow recommended guidelines, but there are some differences between family physicians and other specialists in the drugs chosen for first-line treatment. Family physicians usually kept prescriptions initiated by others, indicating that prescription induction is likely to occur.

Regulatory risk minimization measures were effective in reducing drug use, but there was no decrease in reported adverse drug reactions to nimesulide.

The educational outreach visits trial was implemented with reasonable reach, high dose and very high fidelity and acceptability. Yet the intervention was unsuccessful in improving compliance with guideline recommendations or reducing costs.

Trying to change a physician's prescribing behavior is complex and dependent on many factors that can significantly influence the result of an intervention.

Resumo

Contexto

A literatura médica pode fornecer provas acerca do que devem ser os cuidados de saúde de elevada qualidade. Porém, há um hiato entre os resultados da investigação e a sua aplicação regular na prática clínica. Os médicos nem sempre actuam de acordo com o que estaria de acordo com as melhores provas científicas, mas procurar cuidados de alta qualidade e elevado valor é importante, pois é benéfico para os doentes. As orientações clínicas procuram ajudar os clínicos nesta tarefa, fornecendo resumos com apreciação crítica do melhor conhecimento médico actual e recomendações sobre como os clínicos devem proceder. Porém, os médicos frequentemente falham no cumprimento das recomendações destas orientações. A prescrição médica não é só determinada por conhecimento, competência, relações benefício-risco e custo-efectividade. Outros factores como valores pessoais, crenças, atitudes e experiências, organização dos serviços de saúde, a disponibilidade de informação, características e pedidos dos doentes, interacções entre pares, técnicas de vendas, reciprocidade, autoridade, validação social e relações pessoais são também decisivos. Em certa medida, os médicos de cuidados primários podem ser influenciados por especialistas a prescrever medicamentos que de outro modo não escolheriam.

Muitas intervenções têm sido estudadas com o propósito de melhorar a prática clínica. A maioria das intervenções mostra efeitos pequenos a moderados na melhoria da prescrição. Contudo, há heterogeneidade significativa nos resultados, o que provavelmente reflecte falta de padronização e a interferência de factores específicos do contexto. Duas intervenções específicas são as visitas de divulgação educacional, com o objectivo de mudar o comportamento dos profissionais de saúde através da apresentação de conteúdos educacionais em visitas cara-a-cara; e medidas de minimização de risco por parte das autoridades reguladoras, que procuram melhorar o equilíbrio benefício-risco dos medicamentos depois de terem sido aprovados.

O objectivo geral desta tese é contribuir para a compreensão de como os médicos de cuidados primários decidem prescrever tratamentos com medicamentos e como podem ser influenciados. Os objectivos específicos são descrever como os médicos iniciam o tratamento da hipertensão arterial e da diabetes tipo 2 e se há diferenças entre médicos de família e outros especialistas; avaliar o efeito de acções regulatórias pela Agência Europeia de Medicamentos para restringir a utilização de trimetazidina e nimesulida; e determinar a eficácia e custo-efectividade de visitas de divulgação educacional para melhorar o cumprimento de recomendações em orientações clínicas.

Métodos

Esta tese contém sete manuscritos, divididos em três partes. Os primeiros dois estudos foram estudos transversais aninhados em coorte, realizados dentro da Rede Portuguesa de Médicos Sentinela. Os médicos de família notificaram casos incidentes de hipertensão arterial e diabetes tipo 2, descrevendo o tratamento, quem tinha feito a prescrição inicial e se tinham alterado o tratamento iniciado por outros médicos.

O segundo grupo contém duas análises interrompidas de séries temporais de registos de comparticipação de medicamentos em ambulatório do Serviço Nacional de Saúde Português. Foram medidos os efeitos das medidas de minimização de risco da Agência Europeia de Medicamentos sobre a prescrição de trimetazidina e nimesulida. As acções regulatórias foram identificadas pesquisando as páginas da internet da Agência Europeia de Medicamentos, da Autoridade Portuguesa do Medicamento e da Comissão Europeia. Foram também identificados factores de confundimento no mesmo período. Foram construídos modelos de regressão segmentada para avaliar os efeitos na dispensa de trimetazidina e nimesulida, tanto a nível global como para médicos nos cuidados primários do Serviço Nacional de Saúde, nos hospitais do Serviço Nacional de Saúde e em outros locais. Para a nimesulida, foram também medidas as reacções adversas ao medicamento.

O terceiro grupo contém um ensaio clínico aleatorizado paralelo, aberto, de superioridade, dirigido a médicos de cuidados primários. Os médicos foram recrutados em grupos (clusters) de unidades de cuidados primários e alocados aleatoriamente para receber visitas de divulgação educacional no seu local de trabalho ou a disseminação habitual das orientações clínicas. Os resultados primários foram a proporção de inibidores da ciclo-oxigenase-2 (COX-2) prescrita dentro da classe dos anti-inflamatórios (AINE) e a proporção de omeprazol na classe dos inibidores da bomba de protões aos 18 meses após a intervenção. Os resultados secundários foram a proporção de inibidores da COX-2 dentro da classe dos AINEs a um e seis meses; a proporção de omeprazol na classe dos inibidores da bomba de protões a um e seis meses; e o número de doses diárias definidas de clopidogrel prescritas por 1.000 utentes a 1, 6 e 18 meses. Os dados de prescrição foram recolhidos da base de dados regional de comparticipação. Os custos também foram medidos para realizar uma análise de custo-benefício. O ensaio também foi sujeito a uma avaliação de processo recolhendo dados sobre o recrutamento de médicos e visitantes, registo de um questionário pós-visita, condução de um grupo focal com visitantes, realização de entrevistas a médicos participantes e envio de um questionário para os médicos no grupo de intervenção.

Resultados

Os estudos sobre o tratamento inicial da hipertensão e diabetes mostraram que os médicos de família fizeram a maioria dos diagnósticos e que havia um elevado

cumprimento das recomendações das orientações clínicas em ambas as patologias. Os inibidores da enzima de conversão da angiotensina foram os medicamentos mais usados para iniciar tratamento anti-hipertensor e a metformina foi a mais utilizada na diabetes tipo 2. Algumas diferenças foram observadas entre médicos de família e outros médicos, com os primeiros a prescrever menos beta-bloqueantes e diuréticos de ansa na hipertensão e menos inibidores da dipeptidil peptidase-4 e insulina na diabetes tipo 2. Em ambos os casos, as prescrições iniciadas por outros especialistas raramente foram alteradas pelos médicos de família.

Os estudos sobre a trimetazidina e a nimesulida mostraram diminuições significativas no uso destes medicamentos associadas a intervenções complexas consistindo de medidas regulatórias de minimização de risco e outros factores concorrentes. Contudo, nem todas as acções das autoridades reguladoras levaram a alterações no uso dos medicamentos e factores concorrentes como a cobertura pelos media podem ter desempenhado um papel importante. Os médicos de família foram mais cumpridores das recomendações para restringir a utilização de nimesulida que os médicos dos hospitais ou em actividade privada, enquanto que para a trimetazidina foram menos cumpridores (depois de ajustamento para diferenças na quota de mercado global). Não existiram alterações nos efeitos clínicos adversos para a nimesulida.

O ensaio aleatorizado e controlado das visitas de divulgação educacional foi implementado com sucesso, as visitas decorreram como planeado e foram aceitáveis para os médicos participantes. Contudo, a intervenção não foi efectiva para melhorar os resultados primários ou secundários ou reduzir custos.

Conclusões

Os dois estudos na Rede de Médicos Sentinela mostraram que os médicos maioritariamente seguem as recomendações, mas que existem algumas diferenças entre médicos de família e outros especialistas nos medicamentos escolhidos como tratamento de primeira-linha. Os médicos de família geralmente mantiveram as prescrições iniciadas por outros, indicando que é provável que ocorra indução da prescrição.

As medidas regulatórias de minimização de risco foram eficazes na redução do uso de medicamentos, mas não houve redução nos efeitos adversos reportados para a nimesulida.

As visitas de divulgação educacional foram implementadas com razoável alcance, dose elevada e fidelidade e aceitabilidade muito elevadas. Porém, a intervenção não foi bem-sucedida para melhorar o cumprimento das recomendações de orientações clínicas ou para reduzir custos.

Tentar mudar o comportamento de prescrição de um médico é complexo e dependente de muitos factores que podem influenciar significativamente o resultado de uma intervenção.

Part I – Understanding and changing prescribing behavior

To understand the importance of modifying physicians prescribing behavior one must first comprehend why it is desirable. Medical science can provide evidence on what high quality care should look like. However, there is a gap between research findings and routine clinical practice.[1] Physicians do not always act like what the best scientific evidence would recommend. Loss of efficacy means decreasing health benefits for patients; unsafe practices can increase patient risk; and lack of efficiency results in the use of more resources than would be needed or, in a world with finite resources, choices need to be made. This introduction will detail why healthcare systems should aim for high-quality, high-value care, why physicians need tools such as guidelines to help them reach that goal, reasons for physicians not always following recommendations, what determines medical prescribing and how it can be influenced.

Aiming for high-quality, high-value healthcare

The health of a population is determined to a great extent by social factors like economic status, inequality, education and employment.[2] Providing access to high quality health services is key to reducing the intergenerational perpetuation of inequities.[3] This was done to a large extent in Portugal by creating a public funded National Health Service in 1979, which contributed to reductions in morbidity and mortality and increased life expectancy.[4] Access to high quality care is still an important problem in many parts of the world and, even in highly developed countries in the 21st century, improving access to care has been shown to result in significant gains in mortality and reductions in inequality.[5,6] Aside from being a goal in its own right, better health is also an important tool for a society's economic development by increasing labor productivity, maximizing cognitive development and education, increasing savings, and influencing population numbers and age structure.[7]

However, no human endeavor is perfect, and healthcare systems are no exception. Inequalities remain and result in different health outcomes.[3,4] In part, the full potential of health systems is not realized because resources are limited and may not be used in the most efficient way. High-value care is effective, safe, and cost-conscious.[8] Health systems with higher efficiency achieve better health outcomes with less resources.[9] Inefficiencies can be caused by issues related with the healthcare entity being assessed (from a single treatment to the whole healthcare system, but usually a practitioner or group of practitioners), its links with the rest of the health system (the interaction between several healthcare entities) and external influences (factors outside the control of the healthcare entity).[10] This thesis will focus on physicians as healthcare entities, particularly, their actions as prescribers of drugs.

Population aging in developed countries, economic recession, and increasing costs of new treatments and diagnostic tests place pressure on health systems to

strive for higher efficiency.[11-13] Portugal fulfils all three criteria. Projections estimate a decline from 10.5 to 8.6 million inhabitants between 2012 and 2060 and the aging index rising from 131.1 to 306.5.[14] There were large cuts in the health budget associated with austerity measures, following the financial assistance bailout package agreed with the European Financial Stabilization Mechanism, the European Financial Stability Facility, and the International Monetary Fund.[12] And drug expenses have been rising well above inflation, especially in areas with new drugs, such as HIV/AIDS, oncology and rheumatic diseases for in hospital dispensing and anticoagulants and diabetes in ambulatory care.[15,16]

Decreases in the government's health budget led to a significant increase in private health spending.[12,17] A literature review on the impact of citizen co-payment of drug costs in high-income countries showed increases led to higher health inequalities and caused patients to forego both essential and non-essential drugs.[18] This review found that only two strategies were able to improve efficiency without generating inequality: enabling patients to opt for more cost-effective alternatives and introducing mechanisms to protect poorer people and heavy users of prescription drugs.

When resources are scarce, it is not possible for everyone to have everything and choices need to be made. One important principle in medical ethics is justice, in this case, distributive justice: the extent to which benefits and burdens are distributed among society's members in ways that are fair and just.[19] Justice is fundamental to ensure social cohesion. This principle is reflected on the World Medical Association's International Code of Medical Ethics, which states that a physician shall strive to use health care resources in the best way to benefit patients and their community.[20] Both providing more cost-effective alternatives and introducing mechanisms to protect the disadvantaged are in line with the principle of justice. When it comes to drugs, the first can be achieved by policy actions, such as allowing the patient to opt for generic drugs, and by having prescribers take optimal decisions; the second depends on policies, such as increased reimbursement for specific health problems.

Health technologies assessments can be used to determine if a drug is cost-effective and to compare its effectiveness with other alternatives.[21] This can help guide choices in a world where resources are not infinite. Different approaches have been tried evaluate cost-effectiveness. Currently, one of the most widely disseminated uses quality adjusted life years (QALYs), where the number of years of life gained is multiplied by the quality of life during that time (considering 1 to be perfect health).[22,23] Cost-effectiveness analyses calculate the amount spent for each gained QALY, and this information is then used to guide decisions on allocation of resources.[24] Its main advantage is that it allows for comparison of different treatments and diseases, by transforming their results into a common measure.[25] It also allows society to decide how much it is willing to spend for each QALY.[26,27]

However, QALYs are far from perfect. Major issues include it being very sensitive to the premises that are chosen (like the variation in replies used to calibrate the tool, and their possible lack of representativeness), ignoring individual values (since each person feels their illness differently), considering an average patient (ignoring degrees of severity), and is difficult to use in end-of-life situations.[25,28]

Health technologies assessment is currently used throughout the world by national authorities, including in Portugal.[17,29] These assessments help shape policies, but are not meant to guide decisions by an individual clinician. For the clinician, translating research into actual clinical practice is a complex process and the path has many hurdles that need to be overcome.

The role of guidelines

Medicine is ever evolving, and to keep current with medical literature, a primary care clinician would have to spend every waking minute reading new publications and that still would not be enough.[30] There is a gap between research and clinical practice and one of the major barriers is how much time, effort and skill a clinician needs to access the right information and understand how to use it.[31] Ideally, individual studies would be pooled in systematic reviews, which would be available for clinicians to use and answer every clinical question. This is not the case, as many questions have not been adequately answered by medical literature,[32,33] and time limits the ability of clinicians to search for answers.[34]

Clinical practice guidelines aim to assist clinicians in this task by providing critically appraised summaries of the best current medical knowledge and recommending how to proceed.[35] They have the potential to save the physician from having to find, read and interpret new literature, all while improving quality of care and health outcomes like morbidity, mortality and quality of care.[36-38] However, guidelines also have limitations and disadvantages. Scientific evidence may be lacking or misinterpreted, leading to recommendations that are suboptimal, wrong or, at least, wrong for certain groups of patients.[36] The case of postmenopausal hormone replacement therapy, once recommended as a standard of care based on low quality evidence, should be a reminder of this potential for harm.[39] Guidelines may not take individual patient characteristics into account and the quest for standardization has been criticized by some as having the potential to create "cookbook" medicine.[40] Recommendations may be influenced by the beliefs of the persons writing them and conflicts of interest are frequent in guideline panels.[41,42] They may be designed to serve other priorities than improving patient health, like reducing costs.[36] Guidelines may have low methodological quality,[43] or evidence may not be solid enough to have a common interpretation and lead to conflicting guidelines.[44] The slow pace at which most guidelines are updated may lead clinicians to follow outdated recommendations.[45]

Why physicians do not always follow guidelines

Although most clinicians have a positive attitude towards guidelines,[46-48] having them is not guaranteed to change medical practice. Often, clinicians will fail to follow guideline recommendations,[49,50] even when they self-report doing so.[51] Several reasons have been identified for why this happens.[31,52-54] Physicians may lack knowledge of the guideline, not being aware it exists given the increasing number of guidelines or lacking familiarity with its contents. Physicians may not agree with a guideline because they interpret evidence differently, believe the benefit-risk relation of an intervention is not favorable, that the guideline is not applicable to their population of patients, that it oversimplifies their patients ignoring complexity and multimorbidity, reduces their autonomy and flexibility to make individual decisions, would make the patient-physician impersonal, they distrust the guideline's authors or feel they are biased. Physicians may feel that they lack ability or efficacy to implement guideline recommendations, that the recommendations themselves will not be effective or will not lead to the desired outcomes. Overcoming the inertia to maintain previous practice may be an important issue when physicians lack motivation to implement a guideline. Even when a physician accepts a guideline and wishes to follow it, he or she may forget or neglect to act on it at the appropriate time. The guideline can be considered too complex, lacking adequate summaries, not easy to use, not convenient, cumbersome, vague, confusing or ambiguous. A guideline may be outdated or conflict with a different organization's recommendations. Patients may be barriers to implementing guideline recommendations when their preferences collide with recommendations, they do not understand the need for change or fail to act on the physician's prescribed action (even when they had agreed to it). Finally, there can be external factors such as lack of facilities, staff or time, lack of reminder systems, costs and increased liability.

Some of the barriers mentioned above may be overcome, provided the right causal diagnosis is made and there is an effective implementation strategy.[52]However, how best to make professionals adhere to guideline recommendations is not well established.[55-57]

Determinants of medical prescribing

Medical prescribing is not only determined by knowledge, competence, benefit-risk and cost-effectiveness. Factors such as personal values, beliefs, attitudes and experiences, health services organization, the availability of information, patient characteristics and requests, and peer interactions are also important to shape the prescriber's decisions. [58,59] Marketing techniques, reciprocity, authority, social validation and personal relationships may also play a part in persuading physicians.[31]

A review of studies with primary care physicians found three major influences on prescribing:[60] hospital specialists often act as prescription initiators, which is then maintained by primary care doctors; pharmaceutical representatives are associated with increases in use of new drugs; and prescribing advisors, who help disseminate guidelines. External factors such as the existence of clinical practice guidelines, incentives and quality monitoring programs were also recognized as influential. The cost of drugs was considered in prescribing decisions, but only after efficacy and safety.

A review on adoption of new drugs found that early adoption was not a personal trait of a physician, but varied with the prescriber, patient, practice and drug characteristics.[61] Physician male gender was associated with early adoption of new drugs in seven of fifteen studies included reporting this variable, making this an inconsistent finding. The influence of age was unclear, with most studies reporting a positive association with younger physicians, but others showing no association or even association with older age.

In most studies included in the review, specialists in the therapeutic area of a new drug were more likely to be early adopters than general practitioners or specialists in other areas, but in others studies general practitioners were more often early adopters. Doctors working as clinical trial investigators were more likely to prescribe new drugs, but this decreased with the number of clinical trials the physician had participated. Physicians attending meetings, congresses, conferences and symposia also showed higher adoption of new drugs. Higher prescription volume within the therapeutic class of the new drug, higher total prescription volume and higher prescribing volume of drugs by the same pharmaceutical company were positively associated with early adoption. Having a larger portfolio of drugs prescribed decreased time to adoption.

Pharmaceutical promotion, namely higher marketing budget, detailing, providing samples and direct-to-consumer advertising increased the likelihood of early adoption. The effect of continuous medical education meetings was less consistent. Interactions through social networks such as key opinion leaders and informal interactions with other doctors were positively associated with early adoption. The impact of practicing in a rural or urban area, in a solo or group practice, and the size of the practice were inconsistent and showed no association in most studies.

Excluding drugs specifically designed for the elderly, younger patients were more likely to be prescribed new drugs. Higher patient referral and comorbidities were associated with early adoption of new drugs, as was higher patient socioeconomic status.

Another review, focusing on physicians working in secondary care settings, also found that physicians on Drug and Therapeutic Committees can exert influence on secondary care prescribers; that in patients with more advanced stages of dis-

ease physicians accepted greater risks and used new drugs more; and that physicians who adhere to clinical practice guidelines are less likely to be early adopters than those that use pharmaceutical industry provided information more often.[62]

In Switzerland, allowing physicians to dispense drugs lead to higher costs possibly associated with overprescribing or choosing more expensive options.[63]

Two Portuguese studies used questionnaires and self-reported information sources.[64,65] Pharmaceutical industry was reported as one of the major sources of information in both studies. Results for other sources such as journals and official tools were not consistent. Another study done in Portugal showed that clinicians try to choose drugs with greater proof of effectivity, but that brands also are important in their decision.[66] One study on antibiotic prescribing behavior found that working in the emergency room, seeing more patients, ignoring the link between antibiotic prescribing and resistance, complacency or attributing the responsibility of antibiotic resistance to others were associated with poor quality antibiotic prescribing.[67]

Interventions to modify prescribing

Chochrane's Effective Practice and Organization of Care group has published several systematic reviews on the effect of different types of interventions to modify prescription behavior.[68] Most interventions show small to moderate effects on prescription improvement, but there is considerable heterogeneity in results of the included studies. Heterogenous results probably reflect lack of standardization for each intervention and the interference of setting specific factors.

Dissemination strategies

Physicians may not always be aware and familiar with the most current medical literature and guideline recommendations. Dissemination strategies may be needed to overcome these barriers. A review on continuing education meetings and workshops found they could have a small effect to improve professional practice and patient outcomes.[69] But the authors also concluded that educational meetings alone were not likely to be effective for changing complex behaviors. Strategies to increase attendance at educational meetings could increase their effectiveness.

Using educational games to improve health care professional practice and care for patients was not found to yield consistent results.[70]

Printed educational materials were shown to slightly improve healthcare professional practice, but there was insufficient evidence to estimate their effect on patient outcomes.[71]

Educational outreach visits alone or combined with other interventions were found to have small effects on prescribing, but relatively consistent and potentially

important when hundreds of patients were affected.[72] Effects on other types of professional performance varied from small to modest improvements.

A review on the use of opinion leaders to disseminate and implement evidence-based medicine showed variable effects, from decreased compliance to significant increases.[73] Overall, there was a positive effect, but heterogenous results prevented a solid conclusion.

Designing and providing additional tools along a guideline to improve its implementation led to better compliance with guidelines on non-specific low-back pain and thyroid function tests.[74] However, this strategy has been evaluated in few studies, limiting conclusions on its effectiveness.

Feedback

Providing a practitioner with data on his or her own performance and comparing it to other peers is intended to encourage compliance with professional standards. A review on processes of audit and feedback found that results varied widely across the included studies, ranging from little to no effect to a substantial effect.[75] This strategy was most effective when health professionals were not performing well to start with, the person responsible for the audit and feedback was a supervisor or colleague, the process was repeated more than once, feedback was given both verbally and in writing, and it included clear targets and an action plan.

In-hospital medication review was found to reduce emergency department contacts, but not mortality or readmissions.[76]

Use of enablement (providing advice or feedback) and restrictive (rules to make physicians conform to prescribing guidelines) techniques was shown to be effective in increasing compliance with antibiotic policy and reducing duration of antibiotic treatment in hospital settings.[77]

Decision support technology

Computerized systems have the potential to provide real time advice to a prescriber during a patient encounter. A review on the effect of reminders generated automatically by a computer and delivered to the physician on paper found that reminders improved quality of care slightly overall; that the absolute effect was higher for reminders alone when compared with adding reminders to one or more co-interventions; but it was uncertain if reminders improved patient outcomes.[78]

On screen computer reminders were studied to prescribe specific medications, to warn about drug interactions, to provide vaccinations, or to order tests.[79] They were found to have small to moderate effects achieving improvements in prescriber behavior. Some studies showed larger effects, but there were no specific features consistently associated with larger benefits.

Computerized advice on drug dosage was found to have low quality evidence of improving clinicians' performance to achieve target doses in drugs with narrow therapeutic windows and reducing related patient adverse events.[80]

A review on the effects of telemedicine found studies mostly focusing on diabetes and heart failure.[81] There was some evidence that glucose control, LDL cholesterol and blood pressure could improve in patients with diabetes. There was evidence for reduced admission rates in patients with heart failure and slight improvement in disease-specific quality of life, although there were no differences in mortality. There was limited data for costs and acceptability by patients and health professionals.

Interventions to increase the use of electronic health information by healthcare practitioners, although effective in increasing use of these systems, were not shown to translate into improved clinical practice or patient outcomes.[82]

Financial incentives

Financial incentives have been studied as tools to change how healthcare is delivered. They would act as extrinsic motivation factors for health professionals or organizations. A systematic review providing an overview of this field grouped financial incentives in five areas: payment for working for a specified time period; payment for each service, episode or visit; payment for providing care for a patient or specific population; payment for providing a pre-specified level or providing a change in activity or quality of care; and mixed or other systems.[83] The authors found that payment for working for a specified time period was mostly ineffective; payment for each service, episode or visit, payment for providing care for a patient or specific population and payment for providing a pre-specified level or providing a change in activity or quality of care were usually effective; and there were mixed results on the effectiveness of mixed and other systems. Overall, results showed improvement in processes of care, referrals and admissions and prescribing costs; mixed effectiveness on consultation or visit rates; and no improvement in compliance with guidelines outcomes.

A more recent review focused specifically on the effects of financial incentives on prescribers.[84] It found low quality evidence that pharmaceutical budget caps may lead to a modest reduction in drug use. Evidence for effects of pharmaceutical budget caps on drug costs, healthcare utilization, and health outcomes, pay for performance policies and reimbursement rate policies was of very low quality or non-existent.

A review focusing on methods of payment of primary care physicians found some evidence that the method of payment of primary care physicians affected their behavior, but few studies to make more specific and generalizable conclusions.[85]

Patient directed interventions and policies

Interventions directed at patients or policies affecting patients may indirectly result in changes in health professionals' behavior. A review on the effects of public release of performance data found a small body of evidence and inconsistent results that this intervention resulted in behavior changes of the public, healthcare professionals or healthcare organizations.[86]

A review on the effects of mass media found poor quality evidence that it could have an important role in influencing the use of health care interventions.[87] However, there were no specific conclusions about effects on drug use.

Reference pricing was shown to increase the use of reference drugs and reduce expenditures for insurers.[88] However, the effects on patient's drug expenditures and health were uncertain due to lack of evidence.

Cap and co-payment policies were found to reduce drug expenditure for health insurers, but also to reduce patients' drug use, including life-sustaining and other important drugs for treating chronic conditions, even if these conditions were symptomatic.[89] There was no evidence for health outcomes. Fixed co-payment with a ceiling and tiered fixed co-payment were less likely to reduce the use of essential drugs.

A review on policies that restrict reimbursement aimed at better use of drugs found that, where drugs have cheaper, effective alternatives and they target symptoms, reimbursement restriction polices could ensure better use of drugs with reduced costs and without an increase in the use of other health services.[90] Removing restrictions for drugs used for secondary prevention could result in an intended increase in their use. However, the authors also concluded that policies need to be designed based on good quality research, quantifying the harm and benefit profiles of target and alternative drugs to avoid unwanted health system and health effects, namely impacts on health equity.

Tailored interventions

Tailored interventions are planned after an investigation into the factors that explain current professional practice and any reasons for resisting new practice, and have the potential to yield greater effects since they address the determinants of practice. A review found tailored implementation could be effective, but the effect was variable and tended to be small to moderate.[91] There was insufficient evidence on the most effective approaches to achieve tailoring, including how determinants should be identified, how decisions should be made on which determinants were most important to address, and how interventions should be selected to account for the important determinants.

Research in the thesis

A PhD thesis would not be feasible if it aimed to study all areas related with the determinants of medical prescribing and factors that can modify prescribing decisions. In the following paragraphs, I will limit the scope of research and provide context to the research manuscripts that will be later presented.

Specialist influence in primary care prescribers

The influence of specialist physicians on primary care prescribers is still incompletely understood. Some studies show that specialists are more often earlier adopters, initiating treatments with a new drug, which family physicians then continue.[92-94] When specialists initiate treatment with a different drug, family physicians might feel compelled to keep it, feel they do not have all the information needed to recommend a different treatment or patients might be resistant to change.[95] This could cause part of the family physician's prescribing pattern to be induced by specialists with whom he or she shares patients. Yet this is not always the case, as the same studies show that the rate of adoption varied considerably for different drugs and it was not specialist induced in all case. Clarification of this phenomenon is needed to understand primary care prescribing behavior.

Effect of regulatory actions on drug use

When a medicine is brought to market, knowledge about its benefits and risks is usually incomplete.[96] Often, authorities are later required to take regulatory action regarding safety concerns. Risk minimization measures are meant to improve the benefit-risk balance of drugs after they have been approved.[97] Risk minimization measures may involve requiring additional or more frequent safety studies, changes in approved indications or restrictions on use in certain conditions or patient groups (which are reflected in the summary of product characteristics and patient leaflet), changes to package size, sending educational material to prescribers or patients, or even withdrawal from market.[98] Evaluating the efficacy of risk minimization measures to change actual clinical practice is recommended by the European Medicines Agency (EMA) and the European Parliament. [99,100]

A systematic review evaluated the impact of safety-related regulatory action on clinical Practice.[101] It found that safety regulatory recommendations could modify use of drugs in clinical practice, but there was considerable heterogeneity in outcome measures and analyses across studies, which limited the authors' conclusions. The intended effects were achieved in 57% of the included analyses, were negative in 26% and had mixed effects in 16%. Direct healthcare professional communications, black box warnings and public health advisories had similar impact. Half the studies used before and after designs and the other half used interrupted time-series analyses. The intended effect was reported to have been successful in 72% of before and after studies, but only 41% of the interrupted

time-series designs. None of the studies could rule out the influence of confounding factors.

It is not known why previous studies found such heterogeneous results. Possibly, the type of regulatory intervention, medicine involved and prescriber being targeted are important in determining if an intervention will result in clinical practice changes.

The authors of the review conclude that there is a clear need for further research and make several recommendations regarding future studies. Appropriate study designs are recommended, particularly the interrupted time series, as it allows for greater reliability compared to before and after studies. Other authors agree that interrupted time-series are a reasonable study design to assess the effect of an intervention when identification of a control group is impractical and when interventions are implemented at a clearly defined point in time.[102-104] The estimates of ITS seem comparable to estimates of cluster randomized trials assessing the same research question.[105] They also recommend adequate statistical analysis, including confounding factors in the models. More attention to confounding factors is recommended in general, such as to the effect of media coverage. Intended and unintended effects should be assessed, including impact on the clinical outcomes that were the intended target of the safety warning. It is also recommended that all individual warnings should be assessed and not only a selection, reporting the impact per warning instead of an overall effect.

Educational outreach visits

Educational outreach visits (also known as academic detailing) are aimed at changing healthcare professionals' behavior by delivering educational content in face-to-face visits performed by trained persons (usually another health professional, termed detailer) to health professionals in their own settings.[72]

The process of an educational outreach program has been described by its proponents.[106] It begins with the definition of the areas to be addressed and specific behaviors to be encouraged or discouraged. The outcome of concern should be the highest possible quality of care at the lowest possible cost. Identifying the specific cases of practice that are of highest concern in terms of quality and/or cost could be used to initiate a program. It is then important to understand the motivations for physician behavior. Focus group interviews, surveys and direct communication between detailers and physicians in ongoing programs can be used to this purpose. The next step is to establish credibility for the program. It can be achieved by having the support of neutral professional groups, such as physician associations or academic centers. Programs should then target who prescribe inappropriately or in high volumes to maximize the program's effects. Involving local opinion leaders can help spread and consolidate the program's messages.

During visits, communication by detailers should present both sides of an argument instead of focusing only on the aspects that favor the desired change, as doing so would damage their credibility. Controversial issues should be acknowledged, while providing information that supports the visit's goals. Physicians receiving visits should be actively engaged by inquiring about their opinions, motivations and how their patients reacted to prescribing recommendations. Prescribers should be offered alternatives to the practice being discouraged. Repetition during the visit and reinforcement in follow-up visits are two techniques that should be used. Detailers should be accompanied by graphic print materials that emphasize the main clinical recommendations in a straightforward way.

This detailer is usually a healthcare professional (physician, nurse or pharmacist) with special training in communication skills. He or she presents educational contents previously prepared using the above stated principles. At the end of each visit, details should be recorded to help understand the performance of the program and of that detailer.

Although this was the proposed process, a systematic review found there are currently several ways of conducting educational outreach visits, as some of the components originally described have been altered by different researchers.[72]

The same review concluded that educational outreach visits had a small but consistent effect on improving prescribing behavior, and small to modest improvements in other types of professional performance.[72] It also highlighted several key areas that future research should address. The authors concluded that the long-term performance of educational outreach visits was not known, namely if it deteriorated or improved over time and if multiple visits would be worth the additional cost. Head-to-head comparisons between different educational outreach strategies were recommended, including different types of visitors, contents of visits, and sustained programs versus one-time visits. Studies should be adequately powered to detect the anticipated small effects. Process evaluation should be embedded into trials to assess which components influence the effectiveness of the intervention, if the intervention was fully implemented as intended, and to shed light on the variable effectiveness of educational outreach visits. There could also be contextual factors that lead to variable effectiveness in different subgroups.[107] The review's authors recommend that a realist number of behaviors be targeted for improvement and that investigators clearly indicate a primary outcome. The inclusion of patient outcomes and not only professional performance was also recommended. Finally, economic analyses should be included to measure the use of resources with educational outreach visits.

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Part II – Aim and Objectives

The general aim of this thesis is to contribute to the understanding of how primary care physicians decide to prescribe drug treatments. It is composed of three separate sets of research papers, each focusing on a different aspect of this field and using different methodologies.

The first set is composed of two observational studies which aim to describe how physicians choose to initiate treatment in two chronic conditions very common in primary care: diabetes and hypertension. They report on the drugs chosen as first-line therapy, which physicians are responsible for initiating treatment, if family doctors and specialist physicians have different choices, and if family physicians alter prescriptions initiated by other doctors.

The second set reports on two quasi-experimental studies with the objective of assessing the effect of regulatory actions taken by the European Medicines Agency to restrict the utilization of trimetazidine and nimesulide in real-world use of these drugs. For nimesulide, the study additionally aims to assess the effects on drug-related adverse reactions.

Finally, the third set describes a randomized controlled trial that was designed to compare educational outreach visits with passive guideline dissemination on family physicians' compliance with guideline recommendations and the cost-effectiveness of this intervention. The first manuscript describes the trial protocol in detail. The second reports a process evaluation to analyze the implementation of the intervention regarding reach, dose, fidelity, acceptability of different components of the intervention and perceived impact. The third describes the trial results.

Part III – Physician decisions when prescribing in hypertension and diabetes

Manuscript 1: Initial therapeutic choices for arterial hypertension in the Portuguese Sentinel Practice Network

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Abstract

Background and objectives

Finding which agents are chosen to treat incident cases of hypertension may help interpret prevalent use of anti-hypertensive agents. We aimed to determine the proportion of patients who begin treatment with each anti-hypertensive medicine class, which physicians initiate treatment, if family physicians alter prescriptions initiated by others, and to compare prescribing patterns of family physicians and other specialists.

Methods

Cohort-nested cross-sectional study within the Portuguese Sentinel Practice Network between 2014 and 2015. Family physicians notified incident cases of arterial hypertension reporting treatment, who made the initial prescription and if they had changed treatments initiated by other physicians.

Results

681 incident cases were notified. The initial prescription was made by the patient's family physician in 86.9% (95%CI 84.2-89.3%) of cases. The most used agents were angiotensin converting enzyme inhibitors (51.3% of patients, 95%CI 47.5-55.0%), thiazide and thiazide-like diuretics (32.2%, 95%CI 28.8-35.8%), and angiotensin receptor blockers (21.4%, 95%CI 18.5-24.7%). Compared to other specialists, family physicians used less beta-blockers (20.4 vs 5.9%, $p<0.001$) and loop diuretics (8.2 vs 0.8%, $p=0.003$). Prescriptions initiated by other specialists were changed by family physicians in 11.6% of cases (95%CI 6.0-19.6%).

Conclusion

Angiotensin converting enzyme inhibitors were the most prescribed anti-hypertensive class. Most diagnoses were made by the patients' own family physician. Prescriptions initiated by other specialists were usually continued by family physicians. Prescribing patterns were similar between family physicians and other specialists except for lower use of beta-blockers and loop diuretics.

Keywords

Hypertension; Antihypertensive Agents; Drug utilization; Primary care; Sentinel Surveillance

Introduction

Following the trend in developed countries, hypertension prevalence has been steadily rising in Portugal.[1] This has led to a near doubling in use of antihypertensive medicines, in line with other OECD countries, and a corresponding increase in expenses.[2,3] A report from the Portuguese National Medicines Authority found growing costs were mainly attributable to higher use of angiotensin II receptor blockers (ARBs), despite increased use of generic medicines.[2] Compared with other European countries, use of ARBs was higher in Portugal, where in 2011 there were almost as many prescriptions for ARBs as for angiotensin-converting enzyme (ACE) inhibitors. The same report found that primary care physicians were the prescribing source for 76% of cardiovascular medicines dispensed in ambulatory pharmacies in Portugal; used more ARBs than hospitals, but less than physicians in private practice; and prescribed as much generics as hospitals and more than private practice physicians. In addition to higher cost, ARBs have weaker evidence than ACE inhibitors for reducing morbidity and mortality, although they have fewer withdrawals due to adverse effects.[4,5]

Portuguese guidelines recommend as first-line therapy for patients with low to medium cardiovascular risk: thiazide or thiazide-like diuretics, ACE inhibitors, low cost ARBs, long acting calcium channel blockers, or low dose and low cost fixed dose associations of diuretics with ACEs or ARBs.[6] For patients with high cardiovascular risk, low cost fixed dose associations of thiazide diuretics or calcium channel blockers with ACEs or ARBs are recommended. Beta-blockers are also considered appropriate as initial therapy for younger patients and those with coronary heart disease and certain arrhythmias. The European Society of Hypertension and European Society of Cardiology guidelines state that the main benefits of treating hypertension are due to lowering blood pressure, independently of which medicines are used.[7] Therefore, thiazide and thiazide-like diuretics, beta-blockers, calcium channel blockers, ACEs and ARBs are all considered appropriate as first-line agents. European guidelines recommend lifestyle changes alone for young individuals with isolated elevation of systolic blood pressure and as initial treatment for patients with grade I hypertension at low to moderate cardiovascular risk.

Most studies on antihypertensive medication prescribing focus on prevalent use.[2,8-10] However, this means no conclusions can be drawn about how doctors choose to use each medicine as a first-line agent, as an alternative when initial therapy results in side effects or add-on treatment when the patient fails to achieve

blood pressure goals.[11] Focusing on incident use can determine which medicines are chosen as first-line treatment.

The prescription of ARBs and of thiazide diuretics have been used as quality indicators for primary care in Portugal since 2013.[12] The implicit objective was to decrease ARB use. Although family physicians issue most prescriptions,[2] it is not known how often they are responsible for initiating treatment or maintain prescriptions decided by other physicians. Specialists have been shown to influence primary care physicians by being earlier adopters of new medicines.[13,14]

Determining how anti-hypertensives are used to initiate treatment and who is responsible for their prescription can help guide future quality improvement efforts in the Portuguese National Health Service (NHS). If family physicians have the responsibility for initiating treatment, then quality indicators targeting them may change how anti-hypertensives are used. If, however, most decisions are made by other doctors, targeting only family physicians will probably be ineffective.

With this study, we aimed to determine the proportion of patients with newly diagnosed hypertension who began treatment with each class of antihypertensive medicines. Secondary objectives were to determine which physician was responsible for diagnosing and initiating hypertension treatment, the proportion of cases where family physicians altered prescriptions initiated by other prescribers, and to compare family physicians prescribing patterns with other specialists.

Methods

Study design and setting

The Portuguese NHS is a public funded single payer system, with each citizen being registered in a primary care practice and having an assigned family physician.[15] Some of these family physicians participate as volunteers in the Portuguese Sentinel Practice Network.[16] Each of them contributes with a cohort of their registered patients. This allows the network to have an open cohort of patients that is reasonably stable in each year and it is possible to calculate the incidence of health problems in this sample of the Portuguese population. The network was set up to conduct weekly surveillance of communicable and non-communicable diseases; and it has also been used for observational epidemiological research to answer specific questions (satellite studies).

Between January 2014 and December 2015, the network expanded the information being reported about incidence of hypertension for surveillance purposes, to conduct a continuous notification cross-sectional study among new cases of hypertension notified in the cohort.

Participants

In 2014 and 2015 the population under observation was comprised of 35,535 individuals, distributed among 82 family physicians participating in the Portuguese

Sentinel Practice Network. Participant physicians were asked to notify all incident cases of hypertension. Hypertension was defined using the criteria adopted by the National Health Directorate (systolic blood pressure of 140mmHg or higher or diastolic blood pressure of 90mmHg or higher on several separate occasions).[17]

Measurements

Data was collected using paper or online forms. Notifications included information on patient age at diagnosis, gender, pharmacological treatment (the paper form had a free text field, which was subsequently coded by the investigators into the international non-proprietary name; the online form had a list of antihypertensives available in the Portuguese market by international non-proprietary name, up to three medicines could be entered), other treatment measures (free text field), who had made the initial prescription (the family physician participating in the sentinel practice network or a different physician, who was then specified in a separate free text field; these were later divided in two categories: family physicians and other specialists), and, for prescriptions initiated by other physicians, if the notifying physician had changed the treatment. The Sentinel Practice Network coordinating team followed-up any submissions with incomplete or incoherent information, contacting the notifying physician to gather missing data.

Outcomes

The main outcome in this study was the proportion of patients who initiated treatment with each class of antihypertensive. Classes were defined using the Anatomical Therapeutic Chemical classification categories for C02 antihypertensives, C03 diuretics, C07 beta blocking agents, C08 calcium channel blockers, and C09 agents acting on the renin-angiotensin system.[18]

Secondary outcomes were the proportion of patients where initial diagnosis and therapy were made family physicians (those participating in the Sentinel Practice Network or other family medicine specialists) or other specialists (hospital and private based); the proportion of patients where Sentinel Practice Network physicians altered prescriptions initiated by others; and the proportion of each class of antihypertensives prescribed by family physicians compared with other specialists.

Medicines were compared regarding use as unique treatment combinations in a given patient and total use (as part of any combinations of anti-hypertensive therapy – alone, in fixed dose associations or combined with the administration of other medicines as separate pills).

Study size

To estimate the proportion of patients beginning treatment with each class of antihypertensive medicines with 5% precision and 95% confidence, assuming as a wort case scenario that 50% of patients would begin with a given class, a

minimum sample size of 384 cases of hypertension was calculated. Given the notification rates in previous years of 206 new cases of hypertension per year, we estimated two years of continuous notifications would be needed to achieve our targeted sample size.

Statistical analysis

Proportions of each antihypertensive class prescribed as initial therapy were estimated with their respective 95% confidence interval (95%CI). Patient distribution regarding gender among family physicians and other specialists were compared using Fisher's exact test; age distribution was compared using the T-test. Prescription patterns between family physicians and other specialists were compared using multivariable logistic regression analysis adjusting for patient gender and age. A level of significance (α) of 0.01 was used as the threshold for statistical significance to account for multiple comparisons.

Ethics approval

This study was approved by the Ethics Committee of National Health Institute Doutor Ricardo Jorge (Portugal).

Results

Between 2014 and 2015, 72 family physicians participating in the Portuguese Sentinel Practice Network notified 681 new cases of hypertension. Ten participants did not contribute with any hypertension notifications, but notified other health conditions, hence their patient lists were included to estimate incidence. Hypertension incidence in the cohort was 9.6 / 1.000 person-years. Mean age at diagnosis was 57.0 years (standard deviation 13.2), and 50.1% of patients were male.

Initial diagnosis and prescription was made by the patient's family physician in 592 cases (86.9%, 95%CI 84.2-89.3%), other family physicians in 21 cases (3.1%, 95%CI 2.0-4.7%), other specialists in 49 cases (7.2%, 95%CI 5.5-9.4%) and physicians with unknown specialty in 19 cases (2.8%, 95%CI 1.8-4-3%). There were no statistical differences between family physicians (Sentinel Practice Network participants and other family doctors) and other specialists (excluding unknown specialty) regarding patient age (56.7 vs 60.4 years, p=0.058) or gender (49.1 vs 59.2% male, p=0.19).

Pharmacological treatment was initiated in 95.5% (95%CI 93.6-96.8%) of cases, whereas lifestyle changes alone were introduced in 4.4% (95%CI 3.1-6.2%) and no treatment was reported in one notification. Among patients who were prescribed medicines, lifestyle changes were also prescribed in 50.1% (95%CI 46.3-54.0%).

A single pharmacological substance was used in 68.3% (95%CI 64.6-71.8%) of patients who were prescribed medicines, two substances in 30.3% (95%CI 26.9-34.0%) and three substances in 1.4% (95%CI 0.7-2.7%). No significant differences

were found between family physicians and other specialists in the use of a single substance compared with two or more antihypertensives (69.5 vs 53.1% of patients, p=0.025).

Fixed dose associations were used in 27.9% (95%CI 24.5-31.4%) of patients who were prescribed pharmacological treatment. No differences were seen in the use of fixed dose associations between family physicians and other specialists (27.6 vs 32.7% of patients, p=0.45).

The proportions of each class of antihypertensive agents prescribed as initial therapy are shown in tables 1 (unique treatment combinations) and 2 (total use of each pharmacological class). ACE inhibitors were the most often prescribed medicines, both as single treatment (31.4% of patients) and in total (51.3%). Lisinopril was the most used ACE (32.4% of the class), followed by perindopril (26.1%) and ramipril (21.2%). There were no differences between family physicians and other specialists in use of ACE inhibitors as single treatment (table 1, p=0.38) or in total (table 2, p=0.81).

Thiazide and thiazide-like diuretics were the second most used medicines, with hydrochlorothiazide leading the class (43.9%; always used as part of fixed associ-

Table 1 – Proportion of patients who were prescribed each unique combination of antihypertensive treatment, by class and type of practitioner.

Initial therapy	Family physicians (n=613)	Other specialists (n=49)	Specialty unknown (n=19)	Total (n=681)
	% (95%CI)			
Lifestyle changes alone	4.7 (3.3-6.7)	0.0 (0.0-8.7)	5.3 (0.0-26.5)	4.4 (3.1-6.2)
ACE inhibitor	31.8 (28.3-35.6)	26.5 (16.1-40,4)	31.6 (15.2-54.2)	31.4 (28.1-35.0)
Thiazide-like diuretic	15.3 (12.7-18.4)	2.0 (0.0-11.7)	10.5 (1.7-32.6)	14.2 (11.8-17.1)
ARB	11.9 (9.6-14.7)	10.2 (4.0-22.2)	15.8 (4.7-38.4)	11.9 (9.7-14.6)
ACE inhibitor and thiazide diuretic	10.3 (8.1-13.0)	6.1 (1.5-17.2)	21.1 (8.0-43.9)	10.3 (8.2-12.8)
ACE inhibitor and CCB	7.7 (5.8-10.1)	12.2 (5.4-24.6)	0.0 (0.0-19.8)	7.8 (6.0-10.1)
ARB and thiazide diuretic	6.2 (4.5-8.4)	12.2 (5.4-24.6)	5.3 (0.0-26.5)	6.6 (5.0-8.7)
Beta-blocker	4.7 (3.3-6.7)	12.2 (5.4-24.6)	5.3 (0.0-26.5)	5.3 (3.8-7.3)
CCB	2.1 (1.2-3.6)	2.0 (0.0-11.7)	0.0 (0.0-19.8)	2.1 (1.2-3.5)
ARB and CCB	2.1 (1.2-3.6)	2.0 (0.0-11.7)	0.0 (0.0-19.8)	2.1 (1.2-3.5)
Other	3.1 (2.0-4.8)	14.3 (6.8-27.0)	5.3 (0.0-26.5)	4.0 (2.7-5.7)

ACE – agiotensin-converting enzyme, ARB – angiotensin II receptor blocker, CCB – calcium channel blocker.

ations as it is not available as a single agent in the Portuguese market), followed by indapamide (39.4%) and chlorthalidone (16.7%). No differences were found in the use of thiazide-like diuretics as single treatment (p=0.032) or in total use (p=0.16) between family physicians and other specialists.

ARBs were the third most used medicines as single treatment (table 1) and in total (table 2), with losartan being used most often (30.8% of class), followed by olmesartan (20.5%), valsartan (17.8%) and telmisartan (15.1%). There were no differences between family physicians and other specialists regarding single (p=0.88) or total use (p=0.081).

Calcium channel blockers were rarely used as single treatment (2.1% of patients), but they were the fourth most used class in total (13.1%), with amlodipine being the most prescribed (51.1% of class). Again, no differences were seen between family physicians and other specialists (p=0.93 for single use and p=0.44 for total use).

Beta-blocker was less used by family physicians than other specialists, both as single treatment (4.7 vs 12.2%, p=0.007) and in total (5.9 vs 20.4% of patients, p<0.001). Bisoprolol was the most prescribed beta-blocker (44.7% of class).

Total use of loop diuretics was also lower in primary care physicians (0.8 vs 8.2%, p=0.003). Loop diuretics were used as single treatment in only one case. Potas-

Table 2 – Proportion of patients who were prescribed each class of antihypertensive medicines, by type of practitioner.

Initial therapy	Family physicians (n=613)	Other specialists (n=49)	Specialty unknown (n=19)	Total (n=681)
	% (95%CI)			
ACE inhibitor	51.2 (47.3-55.2)	51.0 (37.5-64.4)	52.6 (31.7-72.7)	51.3 (47.5-55.0)
Thiazide-like diuretic*	32.8 (29.2-36.6)	22.5 (12.9-36.0)	36.8 (19.1-59.1)	32.2 (28.8-35.8)
ARB	20.7 (17.7-24.1)	30.6 (19.4-44.6)	21.1 (8.0-43.9)	21.4 (18.5-24.7)
CCB	13.1 (10.6-16.0)	18.4 (9.8-31.6)	0.0 (0.0-19.8)	13.1 (10.7-15.8)
Beta-blocker	5.9 (4.3-8.0)	20.4 (11.3-33.8)	5.3 (0.0-26.5)	6.9 (5.2-9.1)
Loop diuretic	0.8 (0.3-2.0)	8.2 (2.7-19.7)	0.0 (0.0-19.8)	1.3 (0.1-2.5)
Potassium-sparing diuretic	0.3 (0.0-1.3)	0.0 (0.0-8.7)	0.0 (0.0-19.8)	0.3 (0.0-1.1)
Renin inhibitor	0.0 (0.0-0.8)	0.0 (0.0-8.7)	0.0 (0.0-19.8)	0.0 (0.0-0.7)

* Includes thiazide diuretics. ACE – agiotensin-converting enzyme, ARB – angiotensin II receptor blocker, CCB – calcium channel blocker.

sium sparing diuretics were never reported as single initial treatment, and were only used in combination with other anti-hypertensives in two cases. Direct renin inhibitors were not used as part of the initial treatment for hypertension.

In the 89 cases where treatment was not initiated by physicians participating in the Sentinel Practice Network, there was a change in pharmacological treatment in 10 of patients (11.6%, 95%CI 6.0-19.6%) and information was missing for 3 patients (3.4%).

Discussion

Main findings

The clear majority of patients with newly diagnosed hypertension were prescribed pharmacological treatments. Two thirds of patients were started on a single medicine, with physicians preferring, in decreasing order, ACE inhibitors, thiazide-like diuretics and ARBs. Most patients who were prescribed more than one medicine were started on fixed associations, where ACE inhibitors with thiazide diuretics or with calcium channel blockers were preferred. Loop and potassium sparing diuretics were rarely prescribed in first-line treatments, and there were no reports of direct renin inhibitors use.

Most diagnosis were made by the patient's family physician. Family physicians did not differ significantly from other specialists regarding the use of most classes of anti-hypertensives, but used less beta-blockers and loop diuretics. When other specialists initiated therapy, it usually was continued by family physicians.

Strengths and limitations

By prospectively collecting data within the Sentinel Practice Network cohort we could gather accurate data regarding medicines being prescribed to new cases of hypertension, avoiding recall bias and inaccuracies in administrative data. In most cases, the physician reporting the case was the same who had made the diagnosis and therapeutic decision a few moments before. For cases where the diagnosis had been made by other physicians, information was gathered from patients when they visited their family physicians to request refill prescriptions or for other medical problems. If needed, additional information could be gathered in the patient's national record, which allows the family physician to view details of prescriptions made elsewhere, including by hospital and private physicians (electronic prescription has been mandatory since August 2011 to be eligible for reimbursement by the Portuguese National Health Service).[19] Having this information available to Sentinel physicians greatly reduced patient recall bias in our study.

Some patients might have been diagnosed with hypertension by other physicians and not have visited their family physician during the study period and, therefore, not have been reported to the Sentinel Practice Network. Hence, the incidence of hypertension may be underestimated and the proportion of diagnosis made by

family physicians may be overestimated in our study. However, hypertension incidence was similar to that reported previously in the Sentinel Practice Network,[20] and by authors in other settings.[21] This suggests underreporting was low.

The study did not collect data on disease severity, the presence of comorbidities or contra-indications to specific medicines. These could influence the choice of initial treatment, particularly under Portuguese guidelines. However, gathering such information would have increased the amount of time physicians had to dedicate to each notification and the space needed in paper notification forms. Both would make the study unacceptable to the Sentinel Practice Network. We cannot exclude that patients with more severe clinical situations on initial presentation, such as acute cardiovascular events or heart failure, were more often seen and managed by specialists than by family physicians. This may explain higher prescription of beta-blockers and loop diuretics.

Yet these differences between family physicians and other specialists must be taken as hypothesis generating only. The comparison of prescribing patterns was a secondary outcome in our study and multiple comparisons were made. Despite having used a statistical threshold of 0.01 instead of 0.05 for significance to account for multiple testing, it is still possible that these differences represent false positive results. We did not define a formal adjustment method for multiple comparisons in the study's methods since we could not have known how many combinations of anti-hypertensive treatments would be present in our sample. It is also possible that other differences exist, but our study was underpowered to find them.

Although not statistically significant, there were large absolute differences between family physicians and other specialists in the proportion of men diagnosed, average age at diagnosis, and the proportion of patients treated with a single substance. Our study may have been underpowered to find these differences, as there were relatively few cases diagnosed by other specialists.

Another limitation is that physicians who volunteer to participate in the Sentinel Practice Network might be different than other family physicians, resulting in different prescribing patterns. However, other authors have found these differences to be small.[22,23] Also, given that the observed prescribing patterns for Sentinel physicians and other specialists were similar, it is unlikely that they differ significantly from other family physicians.

Interpretation of results

Previous research on prevalent use of anti-hypertensives had reported greater use of multiple agents, of ARBs relative to ACE inhibitors, of diuretics, calcium channel blockers and beta-blockers.[8,24] A higher use of combination therapy than in our study is to be expected, since an analysis of prevalent use will include patients with longer disease duration. Higher use of diuretics, calcium channel blockers and beta-blockers might be explained by the use of these agents mainly

as add-on therapy when blood pressure goals are not achieved. Our study showed ACE inhibitors to be used almost two and a half times more than ARBs for initial treatment. This is different than what was observed in previous studies on prevalent use and administrative data on drug dispensing, where ACE inhibitors were used less often than ARBs.[2,8,24] Since ACE inhibitors and ARBs are seldom used in combination in the same patient, comparing prevalent use can approximate the relative proportion of patients treated with each of them. Lower prevalent use of ACE inhibitors may indicate that, after initiating treatment, a significant proportion of patients substitute them for other classes like ARBs. It is also possible that prescription patterns have changed since the previous studies and physicians are now preferring ACE inhibitors over ARBs.

Participants in the Sentinel Practice Network usually did not alter medicines initiated by other physicians. This may happen because they agree with the prescription, as our results show no major differences in prescribing patterns of family physicians and other specialists. It is also possible that family physicians feel they do not have enough information to change initiated by specialists, the patient will continue under the responsibility of the other physician or the patient would be resistant to change.[25]

Implications for practice and research

Pharmacological treatment employed a large variety of medicines of different classes, and both family physicians and specialists seem to be following Portuguese and European hypertension guidelines for treating new patients. [6,7] Since use of ARBs is much lower in incident cases than in prevalent patients, future studies should focus on how medicines are used after the initial diagnosis, namely if ARBs are introduced because of adverse reactions, as substitutes or add-on treatment due to lack of blood pressure control with initial therapy or other reasons. If Portugal is to reduce use of ARBs, guidelines should include further recommendations on how to manage patients who are not adequately controlled or who experience adverse reactions with medicines initially prescribed.

Family physicians and specialists had similar prescribing patterns, but the first were the main initiators of anti-hypertensive treatment. Therefore, efforts to improve quality of care in treating hypertension should be mainly directed at family physicians.

Conclusions

The most used medicines classes in incident cases of hypertension were, in decreasing order, ACE inhibitors, thiazide diuretics and ARBs. Most cases were diagnosed by the patients' family physician, but when they weren't, family doctors opted to keep treatments initiated by other physicians most of the time. Prescribing patterns were similar between family physicians and other specialists except for less use of beta-blockers and loop diuretics.

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Declaration of interest statement

The authors declare they have no conflicts of interest.

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Manuscript 2: Initial therapeutic choices for type 2 diabetes in the Portuguese Sentinel Practice Network

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Abstract

Aims

To determine the proportion of new patients with type 2 diabetes who begin treatment with each antidiabetic medicine class, if therapy was initiated by their family physician and if family physicians alter prescriptions initiated by other physicians. To compare prescribing patterns of family physicians and other specialists.

Methods

Cohort-nested cross-sectional study within the Portuguese Sentinel Practice Network. Between 2014 and 2015 family physicians notified incident cases of type 2 diabetes reporting treatment, who made the initial prescription and if treatments initiated by other physicians were changed.

Results

415 incident cases of diabetes were notified. The initial prescription was made by Sentinel Practice Network physicians in 89.4% (95%CI 86.0-92.0%) of cases. Metformin was most often chosen as the first treatment, prescribed to 85.5% of patients (95%CI 81.8–88.6%). Family physicians used less dipeptidyl peptidase-4 inhibitors (4.2% vs 30.3%, p<0.001) and insulin (0.3% vs 12.1%, p<0.001) than other specialists. Prescriptions initiated by others were changed in 4.6% of cases (95%CI 0.4-16.0%).

Conclusions

Metformin was most often chosen as initial therapy. Sentinel Practice Network physicians made the initial prescription in most cases, seldom changed prescriptions initiated by others, and had a different pattern of antidiabetic medicines use than other specialists.

Keywords

Diabetes mellitus type 2; Antidiabetic agents; Drug utilization; Primary care; Sentinel Surveillance

Introduction

Type 2 diabetes pharmacotherapy is one of the major drivers of pharmaceutical spending in Portugal and other developed countries.[1] Rises in expense are partly related to increased diabetes prevalence, but mainly to the greater use of newer and more expensive medicines, such as the dipeptidyl peptidase-4 (DPP-4) inhibitors and insulin glargine.[1,2]

Both international and Portuguese guidelines favour metformin as the first-line agent of choice for most patients with type 2 diabetes after lifestyle changes have been tried.[3,4] Portuguese guidelines prefer a sulfonylurea if metformin is contra-indicated or not tolerated, and recommend insulin if there is markedly symptomatic hyperglycaemia (with glycaemia above 300mg/dL or an HbA_{1C} over 10%).[4] Starting with dual combination therapy is not recommended by Portuguese guidelines, but is considered optional for patients with HbA_{1C} over 9% by the American Diabetes Association and the European Association for the Study of Diabetes joint position statement.[3]

Studies regarding diabetes medicines prescription patterns mainly focus on prevalent use,[1,2,5,6] with only a few identifying the agents used as first-line therapy.[7] Finding which agents are chosen as first-line therapy for new cases of type 2 diabetes may help determine if physicians are following guideline recommendations; and if more expensive agents are being used to initiate treatment or introduced later on (e.g., when initial therapy fails to achieve goals or causes side effects).

Although family physicians account for most diabetes prescriptions in Portugal,[1] it is unknown if new medicines are introduced by them or prescribing is induced by hospital or private practice based specialists. The influence of specialist prescribing of new medicines on primary care physicians has been shown to occur often, but not in all cases. In some studies, specialists are earlier adopters, initiating treatments with a new drug, which family physicians then continue;[8-11] while in other studies family physicians are reported to use new drugs more often.[12]

The main objective of this study was to determine the proportion of new patients with type 2 diabetes who began treatment with each antidiabetic medicine class. Secondary objectives were to determine the proportion of new patients with type 2 diabetes whose initial therapy was prescribed by their family physician, the proportion of cases where family physicians altered prescriptions initiated by other doctors, and to compare family physicians prescribing patterns with private or hospital based specialists.

Methods

Study design and setting

The Portuguese Sentinel Practice Network is composed of volunteer family physicians working in the Portuguese National Health Service (NHS).[13] The Portu-

guese NHS is a single payer public funded system, where each citizen is registered with a family physician.[14] Therefore, each participant in the Sentinel Practice Network contributes with a cohort of their patients. This allows the network to have a reasonably stable cohort each year and calculate incidence of health problems in the Portuguese population. The network collects data for two different purposes: surveillance of communicable and non-communicable diseases for which specified events are systematically reported each week; and epidemiological research that comprises satellite studies, where data is collected to answer a specific question. Only observational research studies are performed within the network.

In 2013, the network agreed to expand the information being collected about incidence of diabetes mellitus for surveillance purposes, to conduct a continuous notification cross-sectional study among new cases of type 2 diabetes notified in the cohort. Data was collected from January 2014 to December 2015.

Participants

In 2014 and 2015 there were 82 active family physicians participating in the Portuguese Sentinel Practice Network, which comprised an observed population of 35,535 individuals. We asked participants to notify all incident cases of diabetes of any age. Diagnosis of diabetes was made using the nationally adopted criteria (the same as those recommended by the World Health Organization in 2006, updated in 2011 to include HbA_{1C}).[15] Only cases of type 2 diabetes were included.

Measurements

Notifications were sent using either online or paper forms. Data were collected on patient age at diagnosis, gender, type of diabetes (type 1, type 2 – only these were included, gestational, other or unknown), pharmacological treatment (the online form had a list of marketed antidiabetic medicines using the international non-proprietary name; the paper form had a free text space; up to three medicines could be entered), other treatment measures (free text), who made the initial prescription (the family physician or another doctor, who was then specified in a separate free text field), and if the initial prescription had been changed by the family physician (only for prescriptions initiated by other physicians). Free text fields were latter coded by the investigators. When incomplete submissions were received, the Sentinel Practice Network coordination contacted the notifying physician to gather missing information.

Outcomes

Our main outcome was the proportion of patients who began treatment with each antidiabetic medicine class. Classes were defined using the Anatomical Therapeutic Chemical classification categories for A10B blood glucose lowering drugs excluding insulins and A10A insulins and analogues.[16]

Secondary outcomes were the proportion of patients whose diagnosis and initial therapy was prescribed by their family physician; the proportion of cases where family physicians altered prescriptions initiated by others; and the proportion of each class of antidiabetics prescribed by primary care physicians (family physicians participating in the Sentinel Practice Network or other family medicine specialists) or private and hospital based specialists.

Study size

We calculated a minimum sample size of 384 cases of type 2 diabetes needed to estimate the proportion of patients beginning treatment with each class of antidiabetic medicines with 5% precision and a 95% confidence interval, assuming as worst case scenario that 50% of patients would begin with one class. Given the previous notification rate, we estimated that two or three years of continuous notification would be needed. To maximize the ability of the network to conduct new projects, we planned to count the number of notifications by the last trimester of the second year and only continue notifications into the third year if the desired sample size had not been achieved.

Statistical analysis

Proportions of each antidiabetic class prescribed as initial therapy were estimated with their respective 95% confidence interval (95%CI). Proportions of medicines prescribed by primary care and non-primary care physicians were compared using Fisher's exact test. A level of significance (α) of 0.01 was used as the threshold for statistical significance to account for multiple comparisons.

Ethics approval

This study was approved by the Ethics Committee of National Health Institute Dr. Ricardo Jorge (Portugal).

Results

During the years 2014 and 2015, 415 incident cases of type 2 diabetes were notified to the Portuguese Sentinel Practice Network by 72 participating family physicians. Ten physicians did not contribute with any diabetes notifications, but, as they notified other health conditions under observation, their patient lists were included when calculating incidence. Having achieved the planed sample size, data collection ended by the end of the second year of the study. Type 2 diabetes incidence in the cohort was 5.8 / 1 000 person-years. Median age at diagnosis was 62 (interquartile range 54 - 71) and 54.5% of patients were male. There were no differences between patients diagnosed by primary care and non-primary care physicians regarding mean age (62.7 vs 60.2 years, p=0.25) and gender (53.7 vs 63.6% male, p=0.28).

The diagnosis and initial prescription was made by physicians participating in the Sentinel Practice Network in 371 cases (89.4%, 95%CI 86.0-92.0%), other

family physicians in 11 cases (2.7%, 95%CI 1.4-4.7%), and other specialists in 33 cases (8.0%, 95%CI 5.7-11.0%).

Lifestyle changes alone were introduced in 12.0% (95%CI 9.2-15.6%) of patients, all were prescribed by Sentinel Practice network physicians. In total, lifestyle changes were prescribed to 65.8% (95%CI 61.1-70.2%) of cases.

In 81.4% (95%CI 77.4-84.9%) of cases patients were started on one single medicine, in 5.8% (95%CI 3.9-8.5%) two medicines were used and in 0.7% (95%CI 0.1-2.2%) three antidiabetics were prescribed. Family physicians used two or more medicines less often than other specialists (4.2 vs 33.3%, p<0.001). Fixed associations were used in 3.4% of cases, less often by primary care physicians than other specialists (2.4 vs 15.2%, p=0.003).

Tables 1 and 2 show the proportion of each antidiabetic class prescribed as initial therapy by family physicians or other specialists grouped by distinct combinations and total class use, respectively. Metformin was used as a single agent or in combinations in 85.5% of patients (95%CI 81.8–88.6%), with no differences between primary care and non-primary care physicians (85.6 vs 84.8%, p=0.801).

Table 1 – Proportion of patients prescribed each distinct combination for initial therapy (by class and type of practitioner). Antidiabetics with and without associated prescription for lifestyle changes are grouped together.

Initial therapy	Family physicians (n=382)	Other specialists (n=33)	Total (n=415)
		% (95%CI)	
Lifestyle changes alone	13.1 (10.1 - 16.9)	0.0 (0.0 - 12.4)	12.0 (9.2 – 15.6)
Biguanides (metformin)	81.4 (77.2 - 85.0)	54.5 (38.0 – 70.2)	79.3 (75.1 – 82.9)
Biguanide and DPP-4-i	2.4 (1.2 - 4.5)	24.2 (12.6 – 41.2)	4.1 (2.5 – 6.5)
DPP-4-i	1.0 (0.3 - 2.8)	6.1 (0.6 – 20.6)	1.4 (0.6 – 3.2)
Biguanide and sulphonylurea	1.0 (0.3 - 2.8)	0.0 (0.0 - 12.4)	1.0 (0.3 – 2.5)
Insulin	0.0 (0.0 – 1.2)	9.1 (2.4 – 24.3)	0.7 (0.1 – 2.2)
Biguanide, sulphonylurea and DPP-4-i	0.5 (0.0 – 2.0)	0.0 (0.0 - 12.4)	0.5 (0.0 – 1.9)
Sulphonylureas	0.3 (0.0 - 1.6)	0.0 (0.0 - 12.4)	0.2 (0.0 – 1.5)
Biguanide and GLP1 agonist	0.0 (0.0 - 1.2)	3.0 (0.0 – 16.7)	0.2 (0.0 – 1.5)
Biguanide and insulin	0.0 (0.0 - 1.2)	3.0 (0.0 – 16.7)	0.2 (0.0 – 1.5)
Biguanide, DPP-4-i and insulin	0.3 (0.0 – 1.6)	0.0 (0.0 - 12.4)	0.2 (0.0 – 1.5)

DPP-4-i - dipeptidyl peptidase-4 inhibitor. GLP1 - Glucagon-like peptide-1. 95%CI – 95% confidence interval.

Table 2 – Proportion of patients prescribed each class as part of their initial therapy (alone or in combinations).

Initial therapy	Family physicians (n=382)	Other specialists (n=33) % (95%CI)	Total (n=415)
Lifestyle changes	68.3 (63.5 – 72.8)	36.4 (22.1 – 53.4)	65.8 (61.1 – 70.2)
Biguanides (metformin)	85.6 (81.7 – 88.8)	84.8 (68.6 – 93.8)	85.5 (81.8 – 88.6)
DPP-4-i	4.2 (2.5 – 6.7)	30.3 (17.3 – 47.5)	6.3 (4.3 – 9.1)
Sulphonylureas	1.8 (0.8 – 3.8)	0.0 (0.0 – 12.4)	1.7 (0.8 – 3.5)
Insulin	0.3 (0.0 – 1.6)	12.1 (4.2 – 27.9)	1.2 (0.4 – 2.9)
GLP-1 agonists	0.0 (0.0 - 1.2)	3.0 (0.0 - 16.7)	0.2 (0.0 – 1.5)

Metformin alone was used more often by family physicians than other specialists (81.4% vs 54.5%, p=0.01). Sulphonylureas alone or in combination were used in 1.7% of cases (95%CI 0.8-3.5%), with no differences between primary care physicians and other specialists (1.8 vs 0.0%, p=1.0). The proportion of patients who began treatment with a DPP-4 inhibitor as a single agent or in combination was 6.3% (95%CI 4.3-9.1%), 4.2% for primary care physicians and 30.3% for other specialists (p<0.001). Insulin alone or in combination was prescribed to 1.2% (95%CI 0.4-2.9%) of cases, by family physicians to 0.3% of patients and by other specialists to 12.1% (p<0.001).

When we excluded cases treated with lifestyle changes alone, the differences between family physicians and other specialists in use of metformin alone (93.7 for family physicians vs 54.5% for specialists, p<0.001), DPP-4 inhibitors (4.8 vs 30.3%, p<0.001) and insulin (0.3 vs 12.1%, p<0.001) as single agents or in combinations, and fixed combination therapy (2.7 vs 15.2%, p=0.005) remained statistically significant. Total metformin use (as a single agent or in combinations) also achieved statistical significance (98.5% vs 84.5%, p=0.001). There were still no differences in sulphonylurea use (2.1 vs 0%, p=1.0).

Among the 44 cases where treatment was not initiated by physicians participating in the Sentinel Practice Network, the prescribed medicines were changed in two cases (4.5%, 95%CI 0.4-16.0%).

Discussion

Main findings

In this study, most cases of type 2 diabetes were diagnosed by family physicians. The majority of patients began treatment with metformin as a single agent, as recommended by Portuguese and international guidelines.[3,4] This occurred more

often when treatment was initiated by family physicians than when initiated by other specialists. Lifestyle changes alone were the initial strategy used by family physicians in about 13% of patients, but in none of the cases diagnosed by other specialists. When these two options are taken together, family physicians managed new cases of type 2 diabetes with lifestyle changes or metformin in 94.5% of cases, compared with 54.5% of cases diagnosed by specialists. Other specialists were more likely than family physicians to use DPP-4 inhibitors, insulin or fixed combinations as their initial choice. Despite these differences, family physicians usually didn't change prescriptions initiated by others.

Sulphonylureas and glucagon-like peptide-1 receptor agonists were seldom used as first-line agents. We observed no use of alpha glucosidase inhibitors, thiazolidinediones or sodium/glucose cotransporter 2 inhibitors for initial therapy.

Strengths and limitations

The main strength of this study is the prospective data collection about therapeutic choices among new cases of diabetes. Almost 90% of cases were reported by the prescribers themselves on the same day or a few days after the diagnosis and a therapeutic decision had been made. For the remaining 10% of cases, Sentinel Practice Network physicians gathered information from the patient or available patient records. In the Portuguese NHS, electronic prescription has been mandatory for reimbursement since August 2011.[17] Information about electronic prescriptions made elsewhere is available to family physicians through the national Health Data Platform.[18] The availability of such information would have limited patient recall bias.

There may have been some cases of type 2 diabetes diagnosed by other physicians that were not reported by participants in the Sentinel Practice Network. However, these should be rare, as the diagnosis of type 2 diabetes grants special benefits to patients in the Portuguese NHS and most would visit their family physician to be entitled to them. Also, incidence during the study period was similar to that previously reported in the cohort (since here we are only considering type 2 diabetes),[19] and to what is reported in other countries (considering these are estimates for the adult population only).[20-22]

It is possible that patients diagnosed by other specialists who were prescribed lifestyle changes alone would not come immediately to their family physician, reporting their diagnosis only when medicines are prescribed. However, when we excluded patients treated with lifestyle changes alone the differences in prescribing pattern did not disappear. Sentinel Practice Network participants could also have underreported lifestyle changes prescribed by other physicians, as patients may have not have valued non-pharmacological treatment and there were no other sources for this information.

We did not collect data on disease severity or presence of contra-indications to specific medicines. Both could influence the decision of initial treatment. However, the number of variables that can be collected in the Sentinel Practice Network is limited, as the paper notification form for all studies in a given year has to fit in one sheet.

Socio-economic status may have been a confounder, as patients with more purchasing power may have been more likely not to use the NHS and also to afford more expensive medicines.

An important limitation is that family physicians participating in the Sentinel Practice Networks might sometimes have different prescribing habits than other family physicians. Participating in a research network is voluntary and could be associated with other physician or patient characteristics that influence prescribing. This has not been thoroughly studied in the Portuguese Sentinel Practice Network, but other authors have found differences to be small.[23,24]

Care must be taken when interpreting differences in use of specific drugs, as we did multiple comparisons, which make false positive results more likely, and this was not the study's primary outcome. Therefore, our findings should be considered mostly as hypothesis generating. Nonetheless, we decided to use a lower than usual threshold for statistical significance (α=0.01 instead of α=0.05) to reduce false discovery rate. A formal adjustment method, such as the Bonferroni correction, was not defined in the study's methods since the number of comparisons to make would be dependent on the number of medicines classes used in our sample. Even so, most of the associations found were very unlikely to be due to chance, with a p value less than 0.001.

Interpretation of results

As expected, metformin was the most frequently prescribed first-line medicine. Second came DPP-4 inhibitors, mainly when used in a fixed association with metformin, with sulphonylureas coming in third place. This goes against recommendations in Portuguese guidelines, which prefer sulphonylureas for having a better cost-benefit relation.[4] It may, however, reflect physician perception of better safety with DPP-4 inhibitors,[25] despite their sparse data on reduction of diabetes complications.[26]

Our findings suggest family physicians prescribe more in line with guidelines than other specialists, who use more intensive pharmaceutical regimens, including newer and more expensive medicines. This may be partially explained by other specialists seeing patients with more severe disease, possibly with symptomatic hyperglycaemia. Since the study did not collect information on disease severity at diagnosis, we are unable to test this hypothesis. Alternatively, specialists might be more willing to use newer medicines or feel more often that their patients do not fit guideline recommendations.[10,27] However, our results are consistent with a

study conducted in the Lisbon region that showed only 17.2% of initial prescriptions for new oral anticoagulant agents originated in primary care.[11]

Family physicians seem to be reluctant to change prescriptions initiated by other specialists. This might be explained by the fact that most these patients would continue to be followed by those specialists. On the other hand, family physicians might feel compelled to keep the treatment initiated by specialists, feel they do not have all the information needed to recommend a different treatment or patients might be resistant to change.[28]

Implications for practice

When considering prevalent prescribing patterns of antidiabetic medicines, policymakers and managers should consider that most patients diagnosed with type 2 diabetes begin with metformin, and probably only escalate to other treatments later in the disease. However, more aggressive initial treatment, including more expensive agents, is more frequent when the diagnosis has been made by specialists. Thus, interventions to reduce inappropriate prescription need to target hospital and private-based specialists and not only primary care doctors.

Future studies should address disease severity at diagnosis, but also when and why patients change their initially prescribed treatment as the duration of diagnosis lengthens and which agents are chosen by physicians then.

Conclusion

Metformin was the agent most often chosen as initial therapy, followed by lifestyle changes alone, fixed combinations of metformin and DPP-4 inhibitors and DPP-4 inhibitors. The diagnosis and initial prescription was made by Sentinel Practice Network physicians in almost 90% of cases. Family physicians changed prescriptions initiated by others in less than 5% of cases. DPP-4 inhibitors and insulin were more likely to be prescribed by other specialists.

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Declaration of interest

Conflicts of interest: none

Contribution statement

DP first developed the study project and wrote the first draft of the manuscript. APR and BN contributed to the conception and design of the study and critically reviewed the manuscript. All authors approve the final version.

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Part IV – The influence of regulatory authorities on prescribers

Manuscript 3: Effect of European Medicines Agency's restrictions on trimetazidine utilization in Portugal

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Abstract

Purpose

Following safety concerns regarding trimetazidine, the European Medicines Agency (EMA) recommended restrictions on its use. Our objective was to determine the impact of regulatory actions on trimetazidine utilization in Portugal.

Methods

Retrospective interrupted time-series analysis of ambulatory pharmacy reimbursement records for the Portuguese National Health Service between January 2006 and December 2015. Regulatory actions were identified by searching the EMA, Portuguese Medicines Authority and European Commission's websites. Confounding factors in the same period were also identified. The main outcome was the dispensing of trimetazidine containing products per month in Portugal.

Results

Two interruption periods were defined in the series: May 2011, when EMA announced it would review trimetazidine safety; and June 2012 to January 2013, when EMA announced it had reached a final opinion recommending restrictions; the European Commission approved EMA's recommendation; the Portuguese Medicines Authority issued safety alerts, changed the summary of product characteristics and approved a direct health-care professional letter; and a regional bulletin was issued.

Interruption 1 had no effect on trimetazidine use, but interruption 2 resulted in decreases in level and trend – from 8.3 million defined daily doses in 2010 to 2.8 million in 2015. After interruption 2, trimetazidine use tended towards a lower steady state.

Conclusions

There was a significant decrease in trimetazidine use in Portugal following a complex intervention that included safety alerts, changes to the summary of prod-

uct characteristics, a direct health-care professional letter and a regional drug bulletin. No effect was seen when EMA announced its review of trimetazidine safety.

Introduction

When a medicine is brought to market, knowledge about its benefits and risks is usually incomplete.[1] Often, authorities are later required to take regulatory action regarding safety concerns. A systematic review concluded that safety regulatory recommendations regarding the use of medicines could modify their utilization in clinical practice.[2] However, it also described considerable heterogeneity in outcome measures and analyses across studies, which limited the authors' conclusions. It is not known why previous studies found such heterogeneous results. Possibly, the type of regulatory intervention, medicine involved and prescriber being targeted are important in determining if an intervention will result in clinical practice changes. The authors recommend further research in this field, with attention to the use of interrupted time series designs, assessment of individual regulatory warnings and decisions, and considering possible confounding factors.

One recent example of safety regulatory interventions targeted trimetazidine in Europe. Trimetazidine was indicated for the prophylactic treatment of angina pectoris and, in some European countries (but not in Portugal), also as ancillary symptomatic treatment for vertigo, tinnitus and visual disturbances due to vascular reasons.[3] However, in 2011, following increased reports of parkinsonism,[4,5] France questioned the European Medicines Agency's (EMA) Committee for Medical Products for Human Use (CHMP) if the marketing authorization for trimetazidine containing medicines should be maintained, altered, suspended or withdrawn, initiating an Article 31 procedure.[3]

The CHMP concluded that the benefit-risk ratio remained positive in angina pectoris if use was restricted to add-on therapy to existing treatments in patients not adequately controlled by or intolerant to other medicines. The Committee recommended that the indications for use in tinnitus, vertigo and visual field disturbances should be removed.[3] Finally, it also concluded that trimetazidine should be contra-indicated in patients with movement disorders and severe renal impairment.[3] This recommendation was adopted by the European Commission in September 2012.[6] The effect of these restrictions in real world clinical use is unknown. Our hypothesis was that trimetazidine use decreased after regulatory intervention and that there were differences in the effects on different types of prescribers.

The objectives for this study were to determine the effect of EMA's recommendation to restrict trimetazidine use on its dispensing in Portugal; and if there were differences in effects by prescriber practice type.

Methods

Study design

Retrospective interrupted time-series analysis of ambulatory trimetazidine use in the Portuguese National Health Service (NHS) using pharmacy reimbursement records between January 2006 and December 2015. Possible confounding factors in the same period were also identified.

Setting

The Portuguese NHS reimburses community pharmacies for 69% of trimetazidine containing medicines costs and the remainder is paid by the patient. Administrative data for mainland Portugal is collected in a central NHS database and anonymized records are made available for research. Inpatient hospital use information was not collected.

Data collection

Trimetazidine utilization

Dispensing information is aggregated by the Portuguese NHS reimbursement database in monthly intervals and includes the international nonproprietary name, dosage, package size, number of defined daily doses (DDDs) in each package (the Anatomical Therapeutic Chemical classification for 2015 was used),[7] number of packages sold and their cost. Data can be analyzed per prescribing site category, which for this study was divided in: NHS primary care, NHS hospitals, and other prescribing sites (mainly physicians in private practice, private hospitals and clinics, and private companies' health services). Prescribing site category data was available since January 2008. Dispensing data was provided by the Portuguese National Medicines Authority - INFARMED - and the Ministry of Health Central Administration.

Regulatory interventions

Regulatory interventions were defined as changes to the summary of product characteristics and patient leaflet, changes to package size or direct communications to prescribers regarding trimetazidine safety. These interventions were proposed by EMA, approved by the European Commission and implemented in Portugal by INFARMED.

EMA and INFARMED press releases, meeting reports and other public communications on the progress of the safety evaluation, but not on a final opinion, were considered as regulatory concurrent factors.

A site-wide search was performed in EMA's, the European Commission's and INFARMED's websites using the international nonproprietary name trimetazidine. We also conducted specific searches in EMA's section on human medicines referrals and INFARMED's sections on safety alerts and health professional directed communications. For EMA and the European Commission, only English

language documents were included. Two authors (AS and DP) classified each result independently as pertaining to trimetazidine safety. Divergences were resolved by consensus.

Concurrent factors

Contextual factors occurring between January 2006 and December 2015 that could have influenced trimetazidine use were collected. These factors were identified by consensus among all study authors when planning the study.

News in general media regarding trimetazidine safety were identified by searching the websites of generalist or news television and radio stations or networks, and the most widely circulated national generalist newspapers and magazines. Specialized media were not included. The search was performed independently by two authors (AS and DP) using both the website's search function and Google (within the website's domain) for the international nonproprietary name or each of trimetazidine's brand names. Each result was classified as pertaining or not pertaining to trimetazidine safety and diverging opinions were resolved by consensus.

Internet searches were measured using the freely available Google Trends tool. Trimetazidine and its brand names were used as key-words and results were restricted to searches in Portugal between January 2006 and December 2015. Data is presented in a scale of 0 to 100, where 100 is the greatest number of total searches.[8] Results for trimetazidine and brand names were added in a total score.

National guidelines and therapeutic bulletins were searched for news regarding trimetazidine safety or recommendations for its use.

The total number of packages dispensed for all reimbursed medicines in community pharmacies by prescribing site category was used to calculate each site's market share.

Outcomes

The main outcome was the number of trimetazidine containing products DDDs dispensed per month in mainland Portugal. The variation of trimetazidine prescriptions originating in each prescribing site category were considered as secondary outcomes.

Statistical analysis

As data for all mainland Portugal was available, no sample size calculations were made. A segmented regression multivariable model was used to analyze changes in level and slope of monthly trimetazidine dispensing between the pre- and post-intervention periods.[9] Regulatory interventions and concurrent factors were tested as predictors in the model: each was considered as an interruption defining a regression segment. All factors were modeled as discrete interventions, except for monthly site market share and internet searches, which were entered as con-

tinuous variables. For each interruption, we included variables for the event, time after event and square time after event when non-linear effects were observed. Interruption periods were censored when calculating the model.

When multiple discrete events occurred less than six months apart, they were modeled as a single interruption. To gain insight on the relative contribution of each event, a sensitivity analysis was conducted replacing the multiple event interruption in the model with each separate event.

Since the relative importance of each prescription site category in providing care for the Portuguese population was not constant during the study period, for secondary outcomes the site's market share for all reimbursed medicines was used as an adjustment variable, to account for global changes in prescription volume within each category.

Autocorrelation was tested using the Durbin-Watson statistic, and, when needed, a Prais-Winsten correction was introduced. A dummy variable for each calendar month was introduced to account for seasonality in the model. Only factors with p values <0.05 were considered statistically significant and retained in the final model. All analyses were conducted using SPSS Statistics software version 23.0 (IBM Corp.), and regression models calculated using the AREG command.

Ethics approval and funding

The study protocol was approved by the Ethics Committee of NOVA Medical School. No external funding was received.

Results

Intervention and concurrent factors timeline

We found 246 results in the European Commission, EMA and INFARMED websites, of which 25 were considered relevant. These are summarized in figure 1. In May 2011 EMA announced that an article 31 procedure had been initiated by France regarding trimetazidine's safety.[10,11] This was labeled interruption 1.

In June 2012 EMA recommended restrictions on trimetazidine use.[12,13] These were accompanied by proposed amendments to the summary of product characteristics and patient leaflet.[14] Simultaneously, INFARMED issued a national safety alert summarizing EMA's recommendations.[15] In July 2012 these recommendations were publicized in EMA's monthly highlights newsletter.[16] In September 2012 the European Commission published a decision supporting EMA's recommendation and concluding the article 31 procedure.[17] EMA then published the procedure report and a questions and answers document.[18,19] In the final decision, the European Commission required changes to the summary of product characteristics and patient leaflet, a direct healthcare professional communication, a safety study to assess the effect of renal impairment and age on trimetazidine pharmacokinetics, a post-authorization safety study to address the identified

risks, and a drug utilization study to verify the compliance of prescribers with the restrictions. INFARMED implemented the first three measures nationally also in September.[20]

In January 2013, the Pharmacy and Therapeutics Committee of Lisbon's Regional Health Administration published a drug bulletin discussing the evidence for trimetazidine use and EMA's opinion.[21] This bulletin was made available on the Regional Health Administration's website and sent as a newsletter to NHS primary care clinicians in the region.

The period between June 2012 and January 2013 was labeled interruption 2, with the regulatory intervention occurring in September 2012.

No news regarding trimetazidine safety were published in major Portuguese media outlets between January 2006 and December 2015. Internet searches are shown in figure 1.

Impact on global trimetazidine use

The number of trimetazidine DDDs dispensed per month increased from a mean 6.9 million in 2006 to 8.3 million in 2010, but decreased to 2.8 million in 2015 – figure 2. Table 1 shows the segmented regression model for trimetazidine dispensing, and the predicted results are superimposed on figure 2. At the beginning of the study period trimetazidine use was increasing, but tending towards a plateau. There were no significant changes in level or trend after interruption 1. After interruption 2 there was a decrease in level, resulting in less 1.6 million

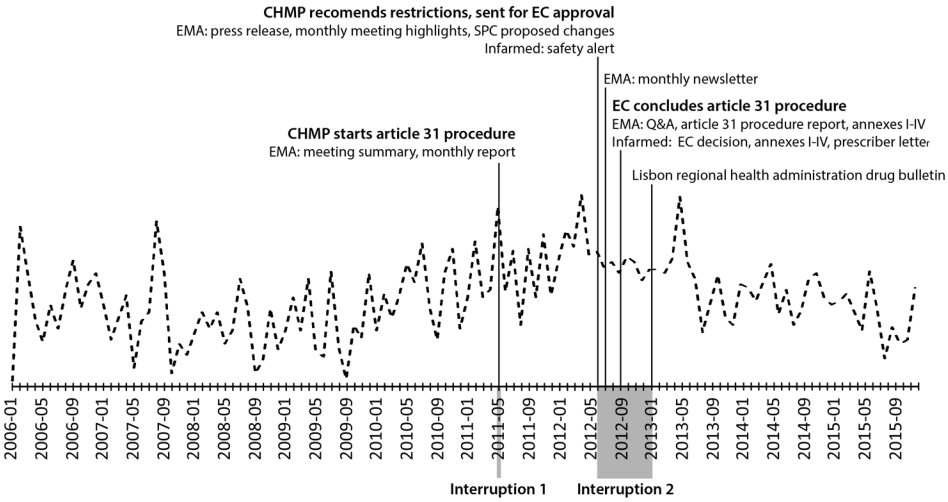

Figure 1 – Interventions and concurrent factors timeline. Vertical lines: regulatory and concurrent events. Dashed line: Google Trends searches. Gray boxes: interruption periods.

DDDs dispensed in the month following the interruption; and a trend to decreasing use (166 thousand DDDs less for each month after the interruption), but attenuating over time and tending towards a plateau (3 thousand DDDs more for each month squared after the interruption). Internet searches were not a significant predictor. Seasonal effects were observed for the months of February, April, August and November.

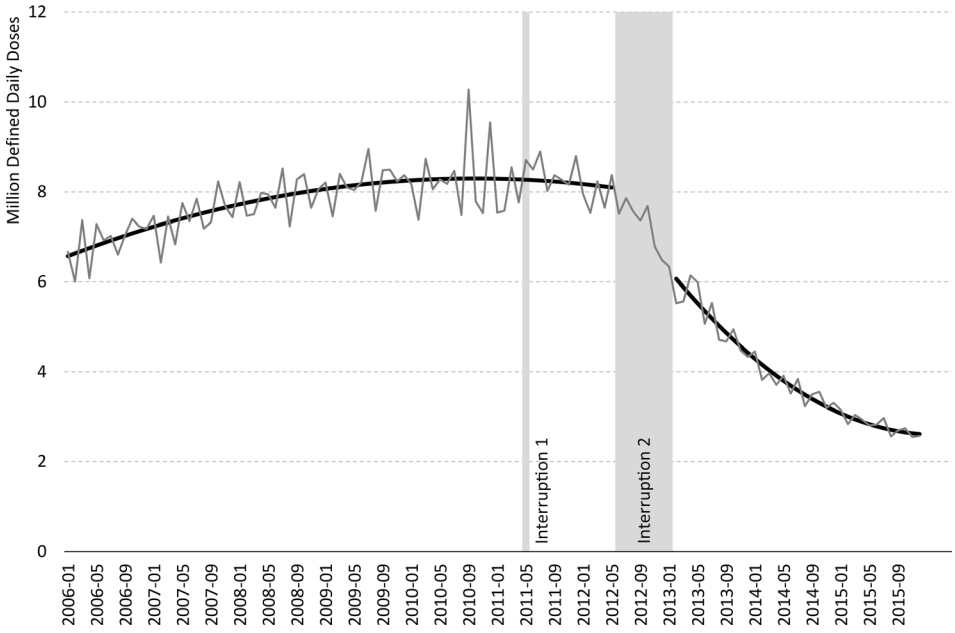

Figure 2 – Global trimetazidine use. Gray line: observed dispensing of trimetazidine (millions of defined daily doses per month). Black line: segmented regression model.

Table 1 – Segmented regression model for global trimetazidine use. Effect estimated in defined daily doses. Adjusted for seasonal variation. Model R^2=0.988.

Variable	Effect estimate (95% CI)		p value
Intercept	6 660 306.6	(6 492 683.8, 6 827 929.3)	<0.001
Time†	61 963.7	(52 607.4, 71 320.0)	<0.001
Time squared†	-536.7	(-653.1, -420.3)	<0.001
Interruption 2‡	-1 638 746.6	(-1 974 524.6, -1 302 968.6)	<0.001
Time after interruption 2‡	-166 339.0	(-199 318.4, -133 359.6)	<0.001
Time after interruption 2 squared‡	3 150.6	(2 294.1, 4 007.1)	<0.001

† January 2006 = 1. ‡ February 2013 = 1.

Sensitivity analysis considering each separate event within interruption 2, showed best fit for the model considering the announcement of CHMP recommendations for restricted use of trimetazidine in June 2012 (adjusted $R^2 = 0.987$; see table A1 in the appendix). However, in this model changes in level were not significant, only those in trend. When the European Commission's decision and national implementation were used, the model had similar performance (adjusted $R^2 = 0.986$, table A2), but changes in level became significant. The worst performing model was the one considering the publication of a Lisbon regional health administration drug bulletin (adjusted $R^2 = 0.979$; table A3).

Impact on trimetazidine use by prescribing site

Between 2008 and 2015, most trimetazidine prescriptions originated in NHS primary care (72.7%), followed by other prescribing sites (22.0%), and then NHS hospitals (5.3%). Trends before interruption 1 were different among these sites (figure 3): NHS primary care and other prescribing sites had reached a peak by 2010, while use in NHS hospitals continued to grow. Interruption 1 corresponded to a jump in NHS hospitals use of 23.8 thousand DDDs (a 6% relative increase) compared to what was expected had the intervention not occurred (table 2). However, interruption 1 was not significant for NHS primary care or other prescribing sites.

Interruption 2 was associated with a decrease in level and slope for all sites, but the later attenuated over time. Comparing the six months before interruption 2 with those that followed, trimetazidine monthly use decreased from 6.1 to 4.0 million DDDs in NHS primary care (-34.1%), from 444 to 319 thousand DDD in NHS hospitals (-28.0%), and from 1.5 to 1.3 million DDDs in other sites (-15.2%). Average dispensing in the second half of 2015 had decreased to 1.8 million DDDs in NHS primary care (-70.9%), 155 thousand DDDs in NHS hospitals (-65.0%) and 749 thousand DDDs in other sites (-50.0%).

However, in the same period, the relative importance of each site for the provision of care in Portugal was not constant, as shown by each site's market share on global dispensing of medicines – figure 3. We estimate that, had each site's global market share remain at a constant level (January 2008 to April 2011 average), trimetazidine use in the second half of 2015 would have been 2.6 million DDDs

Figure 3 (oposite) – Trimetazidine use by prescribing site. Panel A – NHS primary care, panel B – NHS hospitals, panel C – other prescribers. Solid gray line: observed dispensing of trimetazidine (millions of defined daily doses per month). Dotted gray line: global medicines market share (percent). Solid black line: regression model considering average global market share in the segment. Dashed black line: regression model considering global market share remained constant (January 2008 to April 2011 average).

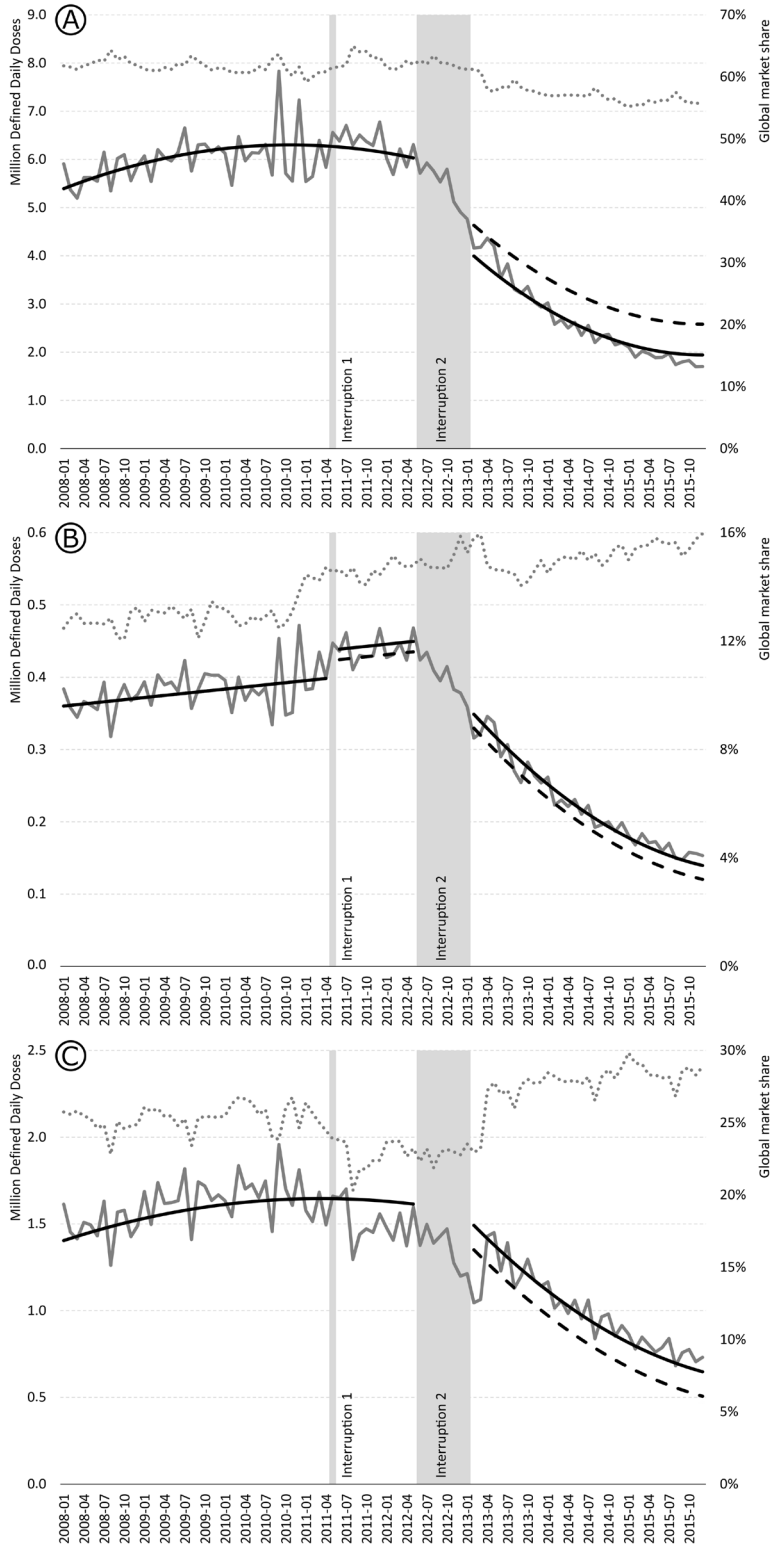
A
Million Defined Daily Doses
Global market share
Interruption 1
Interruption 2
B
Million Defined Daily Doses
Global market share
Interruption 1
Interruption 2
C
Million Defined Daily Doses
Global market share
Interruption 1
Interruption 2

Table 2 – Segmented regression model for trimetazidine use by prescribing site category. Effect estimated in defined daily doses.

Variable	Effect estimate (95% CI)		p value
NHS Primary Care – model R^2=0.988¶			
Intercept	-3 285 767.3	(-6 580 924.9, 9 390.3)	0.101
Time†	55 555.1	(41 943.0, 69 167.3)	<0.001
Time squared†	-801.7	(-1 048.2, -555.2)	<0.001
Interruption 2‡	-959 212.6	(-1 317 601.6, -600 823.5)	<0.001
Time after interruption 2‡	-81 582.0	(-116 848.6, -46 315.4)	<0.001
Time after interruption 2 squared‡	2 565.1	(1 879.7, 3 250.6)	<0.001
Global market share (proportion)	14 045 680.3	(8 799 302.6, 19 292 058.0)	<0.001
NHS Hospitals – model R2=0.982¶			
Intercept	275 692.0	(195 076.0, 356 308.0)	<0.001
Time†	978.5	(600.8, 1 356.1)	<0.001
Interruption 1§	23 778.9	(11 525.7, 36 032.0)	0.002
Interruption 2‡	-103 203.7	(-117 646.4, -88 761.1)	<0.001
Time after interruption 2‡	-11 310.4	(-12 943.1, -9 677.8)	<0.001
Time after interruption 2 squared‡	116.0	(73.6, 158.4)	<0.001
Global market share (proportion)	907 915.8	(257 425.1, 1 558 406.5)	0.02
Google searches score	-361.1	(-573.6, -148.5)	0.006
Other prescribers – model R^2=0.970¶			
Intercept	71 852.5	(-268 216.4, 411 921.3)	0.73
Time†	12 995.5	(8 973.4, 17 017.5)	<0.001
Time squared†	-165.6	(-249.4, -81.9)	0.002
Interruption 2‡	-213 125.9	(-332 948.1, -93 303.6)	0.004
Time after interruption 2*‡	-32 608.4	(-45 008.3, -20 208.6)	<0.001
Time after interruption 2 squared‡	582.2	(384.3, 780.1)	<0.001
Global market share (proportion)	5 822 791.3	(4 403 067.2, 7 242 515.3)	<0.001
Google searches score	-1 288.8	(-2 217.0, -360.5)	0.024

† January 2008 = 1. ‡ February 2013 = 1. § May 2011 = 1. ¶ Adjusted for seasonal variation.

in NHS primary care (-57.7% than in the six months before interruption 2), 127 thousand DDDs in NHS hospitals (-71.5%) and 537 thousand in other sites (-64.1%).

Seasonal effects were observed among all sites. Google searches were inversely associated with trimetazidine prescription in NHS hospitals and other sites.

Discussion

We examined trimetazidine dispensing in Portugal before, during and after the European Medicines Agency recommended restrictions to its use. A complex regulatory intervention was associated with a reduction in trimetazidine use, which by 2015 had declined to about one third the average use in 2011.

Between 2006 and 2015 we documented two interruption periods. In May 2011, EMA's announcement of an article 31 procedure caused no effect on global trimetazidine use. As the national authority issued no communications to prescribers or the public, there was no media coverage and it is not expected that most practicing clinicians regularly visit EMA's website, prescribers and patients were probably unaware trimetazidine's safety had been questioned.

During interruption 2, there was a sharp decrease in trimetazidine dispensing. National safety alerts and a direct to health-care professional communication probably had an important role making physicians aware of EMA's recommendations. A regional bulletin on trimetazidine safety seems to have been published when most changes had already taken place, but may have helped consolidate the trend.

All prescribing site categories showed decreased trimetazidine use. The relative reduction was highest for NHS primary care both in the six months after the intervention and by late 2015, and lowest for other sites. However, when adjusted for the total amount of medicines being prescribed in each site category, NHS primary care had the lowest relative reduction and NHS hospitals the highest. This highlights the need to consider global changes in context when analyzing effects by prescriber type.

In the years following interruption 2, the trend to decreased trimetazidine use continued, suggesting some physicians were late adopters of the recommendations. However, by 2015, dispensing was tending towards a new steady state. This may indicate that only patients meeting EMA's recommendations were being prescribed trimetazidine by then or that most physicians willing to change their practice had done so. Since data on individual patients or physicians was not collected, we are unable to verify these hypotheses.

Changing the package leaflet was the only intervention targeting patients that we could identify. No media coverage of trimetazidine safety was found during this period and there was no clear pattern showing changes in Google searches around interruption 2. The significance of the inverse association of trimetazidine use with Google searches in NHS hospitals and other sites is unclear, as it was not present in the global model and Google searches fluctuated throughout the study period. It is unlikely that patients had a major role in the reduction of trimetazidine use.

A systematic review found direct healthcare professional communications and black boxed warnings to be effective in achieving the intended effect 56% and 57% of cases, respectively.[2] Our results are concordant with a positive effect for these regulatory interventions. However it should be noted that black boxed warnings are not the same as changes to the summary of product characteristics and patient leaflet, and our study considered the effects of these interventions together.

We aimed to address some of the key recommendations from the mentioned systematic review on the impact of safety related regulatory action: to use an interrupted time series design (ITS), include confounding factors and assess impact for each individual warning.[2] ITS are a reasonable study design to assess the effect of an intervention when identification of a control group is impractical and when interventions are implemented at a clearly defined point in time.[22-24] The estimates of ITS seem comparable to estimates of cluster randomized trials assessing the same research question.[25] In our analysis we tried to account for several concurrent effects, although there may have been other influences on both physicians and patients that we have not collected. We were unable to measure the impact in clinical outcomes or assess if trimetazidine discontinuation only happened in patients with indications that were removed. We also could not distinguish among several interventions happening during interruption 2 as there were not enough data points between them to estimate a regression segment with reasonable confidence. It is possible that these interventions had different impact among prescribers, but we cannot determine how each factor contributed to the overall result and how they interacted with each other. Finally, we could not study unintended effects, namely, if there was substitution with other drugs.

In conclusion, we found a significant decrease in trimetazidine use from 8.3 to 2.8 million DDDs per month, following a complex intervention that included safety alerts, changes to the summary of product characteristics a direct healthcare professional letter and a regional drug bulletin. No effect was seen when EMA announced it would begin to review trimetazidine safety. The individual impact of each component and the importance of the order in which they were used remains unknown.

Acknowledgments

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Conflict of Interest statement

The authors declare they do not have conflicts of interest regarding this manuscript.

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Appendix

Sensitivity analysis for global trimetazidine use

The following tables show alternative segmented regression models for global trimetazidine use if the events in interruption 2 are considered separately. Event 1 took place in June 2012 (see figure 1 and results in the main text). EMA's monthly newsletter on July 3rd is considered together with event 1, since it was published so early in the month. For event 1, June data was censored and July is considered the first month after the interruption (table A1). Similarly, event 2 took place in September (table A2) and event 3 in January 2013 (table A3), therefore October 2012 and February 2013 were respectively considered the first month after the interruption.

Table A1 – Segmented regression model for global trimetazidine use using EMA's recommendation for restrictions as interruption 2 (see figure 1). Effect estimated in defined daily doses. Model R^2=0.987.

Variable	Effect estimate (95% CI)		p value
Intercept	6 662 082.0	(6 495 085.7, 6 829 078.4)	<0.001
February	-786 816.1	(-1 001 622.7, -572 009.6)	<0.001
April	-346 599.9	(-561 409.0, -131 790.8)	0.002
August	-421 468.6	(-635 901.4, -207 035.8)	<0.001
November	-252 107.8	(-466 576.8, -37 638.7)	0.022
Time†	61 837.9	(52 458.6, 71 217.3)	<0.001
Time squared†	-532.9	(-649.4, -416.4)	<0.001
Interruption 2‡	-49 399.0	(-328 363.7, 228 485.7)	0.723
Time after interruption 2‡	-235 312.6	(-260 629.5, -209 995.6)	<0.001
Time after interruption 2 squared‡	3 603.0	(3 045.9, 4 160.2)	<0.001

† January 2006 = 1. ‡ July 2012 = 1.

Table A2 – Segmented regression model for global trimetazidine use the European Commission's decision and national implementation by INFARMED as interruption 2 (see figure 1). Effect estimated in defined daily doses. Model R^2=0.986.

Variable	Effect estimate (95% CI)		p value
Intercept	6 615 465.1	(6 445 484.2, 6 785 446.0)	<0.001
February	-748 449.7	(-969 449.0, -527 450.4)	<0.001
April	-310 946.4	(-531 600.7, -90 292.1)	0.006
August	-427 874.0	(-648 348.6, -207 399.4)	<0.001
November	-217 653.0	(-440 503.5, 5 197.5)	0.056
Time†	65 492.7	(56 286.8, 74 698.7)	<0.001
Time squared†	-590.1	(-700.2, -480.0)	<0.001
Interruption 2‡	-692 441.7	(-988 404.9, -396 478.5)	<0.001
Time after interruption 2‡	-199 186.9	(-228 334.1, -170 039.6)	<0.001
Time after interruption 2 squared‡	3 469.8	(2 776.9, 4 162.7)	<0.001

† January 2006 = 1. ‡ October 2012 = 1.

Table A3 – Segmented regression model for global trimetazidine use using Lisbon Regional Health Administration's drug bulletin as interruption 2 (see figure 1). Effect estimated in defined daily doses. Model R^2=0.979.

Variable	Effect estimate (95% CI)		p value
Intercept	6 514 374.4	(6 313 727.0, 6 715 021.7)	<0.001
February	-739 156.1	(-990 081.7, -488 230.5)	<0.001
April	-289 143.0	(-539 568.2, -38 717.8)	0.024
August	-460 835.2	(-710 696.1, -210 974.2)	<0.001
November	-351 781.9	(-602 598.1, -100 965.7)	0.006
Time†	75 673.6	(65 240.9, 86 106.2)	<0.001
Time squared†	-740.8	(-859.6, -621.9)	<0.001
Interruption 2‡	-1 251 566.6	(-1 623 770.4, -879 362.8)	<0.001
Time after interruption 2‡	-137 991.4	(-179 203.1, -96 779.7)	<0.001
Time after interruption 2 squared‡	3 194.2	(2 104.6, 4 283.7)	<0.001

† January 2006 = 1. ‡ February 2013 = 1.

Manuscript 4: Effect of European Medicines Agency's Regulatory Measures on Nimesulide Utilization in Portugal

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Abstract

Purpose

Severe hepatic adverse events led the European Medicines Agency to recommend restrictions on nimesulide use. Our aim was to determine their effect on nimesulide dispensing in Portugal.

Methods

Interrupted time-series using pharmacy billing records of the Portuguese National Health Service. Regulatory actions, concurrent events and nimesulide dispensing were recorded from 2006 to 2015. The primary outcome was the number defined daily doses (DDD) of nimesulide dispensed per month. Secondary outcomes were the number of adverse reactions to nimesulide, and the variation of nimesulide prescriptions by prescribing site category.

Results

We found three possible interruption periods: 1) May 2007 to March 2008: nimesulide was withdrawn from Ireland, the European Medicines Agency initiated a safety review and this was reported by Portuguese media; 2) October 2009 to April 2010: the European Commission reached a decision and mandated a broader safety review; and 3) December 2010 to April 2012: the Commission's decision was implemented in Portugal, the broader safety review was concluded and implemented. Nimesulide use showed a declining trend at the start of the series (-12.2 thousand DDD/month). Interruptions 1 and 3 were associated with decreases in level (-824.7 thousand and -449.0 thousand DDD, respectively). Interruption 3 was associated with a greater decrease in primary care than in other sites. The number of reported adverse events did not decrease.

Conclusions

Nimesulide use decreased significantly following two complex interventions including regulatory measures, media reports and other concurrent factors. However, this was not associated with a decrease in reported adverse drug reactions.

Key words

Drug regulation, physicians practice patterns, nimesulide.

Introduction

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) marketed in more than 50 countries worldwide.[1,2] Since being first authorized in 1985,[3] it has been associated with an increased risk of severe hepatotoxicity, which led to its withdrawal in some countries (Finland and Spain in 2002) and restrictions on its use in others.[2]

In May 2007, the Irish Medicines Board suspended marketing authorizations after several cases of fulminant hepatic failure.[4] This prompted the European Medicines Agency (EMA) to review nimesulide's safety, resulting in recommendations for restricted use.[1,2] Yet, the efficacy of these recommendations is unknown.

Risk minimization measures are meant to improve the benefit-risk balance of drugs after they have been approved.[5] A systematic review found mixed results, with intended effects varying among different drugs and regulatory measures.[6] Overall, the intended effect of regulatory measures was successful in 56% of the analysis, but only in 41% of the analysis using an interrupted time series design. The authors concluded there was a clear need for more research to understand the effect of safety warnings, highlighting the need to assess the impact on both drug utilization and the outcomes intended by regulatory measures, the use of appropriate study designs (the interrupted time series being preferred) and to consider the impact of confounding factors on measured outcomes.

We aimed to assess the effect of risk minimization measures adopted at European level on the nimesulide utilization and nimesulide-related adverse drug reactions in Portugal from 2006 to 2015.

Methods

Study design

Retrospective interrupted time-series analysis using pharmacy billing records of the Portuguese National Health Service (NHS) for oral NSAIDs between January 2006 and December 2015, considering possible confounders during this time. Clinical outcomes were measured using the national adverse drug reactions registry.

Setting

Community pharmacies are reimbursed by the Portuguese NHS for 37% of the cost of oral NSAIDs. To be reimbursed, pharmacies are required to send dispensing data to the Ministry of Health. This is collected in an anonymized database and made available for research purposes. It does not include information regarding inpatient hospital use, the Azores and Madeira islands (which have an autonomous health system) or non-reimbursed drugs.

Data collection

Regulatory interventions

Regulatory interventions were defined as actions mandated by regulatory authorities on market authorization holders. Interventions were proposed by EMA, adopted by the European Commission and implemented by the Portuguese Medicines Authority (INFARMED). Regulatory concurrent factors were defined as public communications by any of these institutions, reporting that nimesulide safety was under scrutiny.

We conducted site-wide searches for the international nonproprietary name nimesulide in the European Commission, EMA and INFARMED websites, and specific searches in EMA's section on human medicines referrals and INFARMED's sections on safety alerts and health professional directed communications. Only English language results were included in the European Commission and EMA's websites. Results were classified by two authors (DP and AS) as relating to nimesulide's safety. Changes to the summary of product characteristics were monitored using INFARMED's publicly available drug database.

Concurrent factors

Potential factors that may have influenced nimesulide use were identified by consensus among all study authors at the planning stage.

Total NSAIDs dispensing was used to control for global market and site variations. NSAID dispensing data was used to identify market entry and exit of drugs, as prescriptions could have transferred from or to nimesulide, respectively. These were considered as possible concurrent factors if they had a peak market share of at least 5% of the NSAID class.

Media coverage was identified by searching for news containing the international nonproprietary name nimesulide or one of its brands. The search was conducted independently by two authors (DP and AS) in generalist or news television stations or networks, radio stations, and most widely circulated national newspapers and magazines. Specialized media were excluded. Each media outlet website's search function and Google search limited to the website's domain were used. Results were classified as relating or not to nimesulide safety, and the later were excluded.

Google trends was used to measure internet searches for nimesulide or its brand names in Portugal. Results are presented in relative scale of 0 to 100, where 100 is the greatest number of total searches in a location during the period.[7] Searches for nimesulide and brand names were added in a total score.

Estimates for the incidence of influenza-like illness in Portugal were considered, as nimesulide was used for many years to treat its symptoms. Incidence data was provided by the Portuguese Sentinel Practice Network. However, influenza-like illness was introduced as a contraindication during the study period. Therefore, this variable was divided into two by multiplying the incidence by two dummy variables (one with value 0 before the contraindication and 1 after and the other with these values reversed). This allowed us to calculate two separate beta coefficients for influenza like illness incidence: before and after the contraindication.

Prescription data

Data on NSAID dispensing was provided to the authors by INFARMED and the Ministry of Health Central Administration. Dispensing information is compiled in monthly intervals and includes the international nonproprietary name, dosage, package size, number of defined daily doses (DDD) in each package (the Anatomical Therapeutic Chemical classification for 2015 was used), number of packages sold and their cost. Data by type of prescribing site is available since 2008, which for this study was categorized in: NHS primary care, NHS hospitals and other prescribing sites (mostly, private care).

Adverse drug reactions

INFARMED provided the authors with national pharmacovigilance data regarding adverse drug reactions for nimesulide containing substances. Information was available on date of notification, severe / non-severe categorization, and reaction group categorization using the MedDRA dictionary of terms. These were then divided by the authors in severe hepatobiliary, other severe and non-severe reactions and grouped in years.

Outcomes

The primary outcome was the number of nimesulide containing products DDD dispensed per month. Secondary outcomes were the number of adverse reactions to nimesulide containing products, and the variation of nimesulide prescriptions originating in each prescribing site category.

Statistical methods

No sample size calculation was made, as data for the whole NHS was available. Data was analyzed using a segmented regression multivariable model to test for changes in level and/or trend in nimesulide dispensing in the pre- and post-intervention periods.[8] Regulatory and concurrent factors were tested as predictors of nimesulide dispensing. Discrete events occurring less than six months apart were

modeled as the same intervention. For each intervention, we included variables for the event, time after the event and square time after the event to account for non-linear effects. Total NSAID use, Google search trends, and influenza-like illness incidence were treated as continuous variables.

The model was tested for autocorrelation using the Durbin-Watson statistic, introducing a Prais-Winsten correction if needed. Seasonality was modeled by introducing a dummy variable for each calendar month.[9] Only factors with p values <0.05 were retained in the final model. Analyses were done using SPSS Statistics software version 23.0 (IBM Corp.) using the AREG command.

Ethical approval and funding

This study was approved by the Ethics Committee of NOVA Medical School. No data on individual patients, physicians or health care practices was collected. There was no external funding.

Results

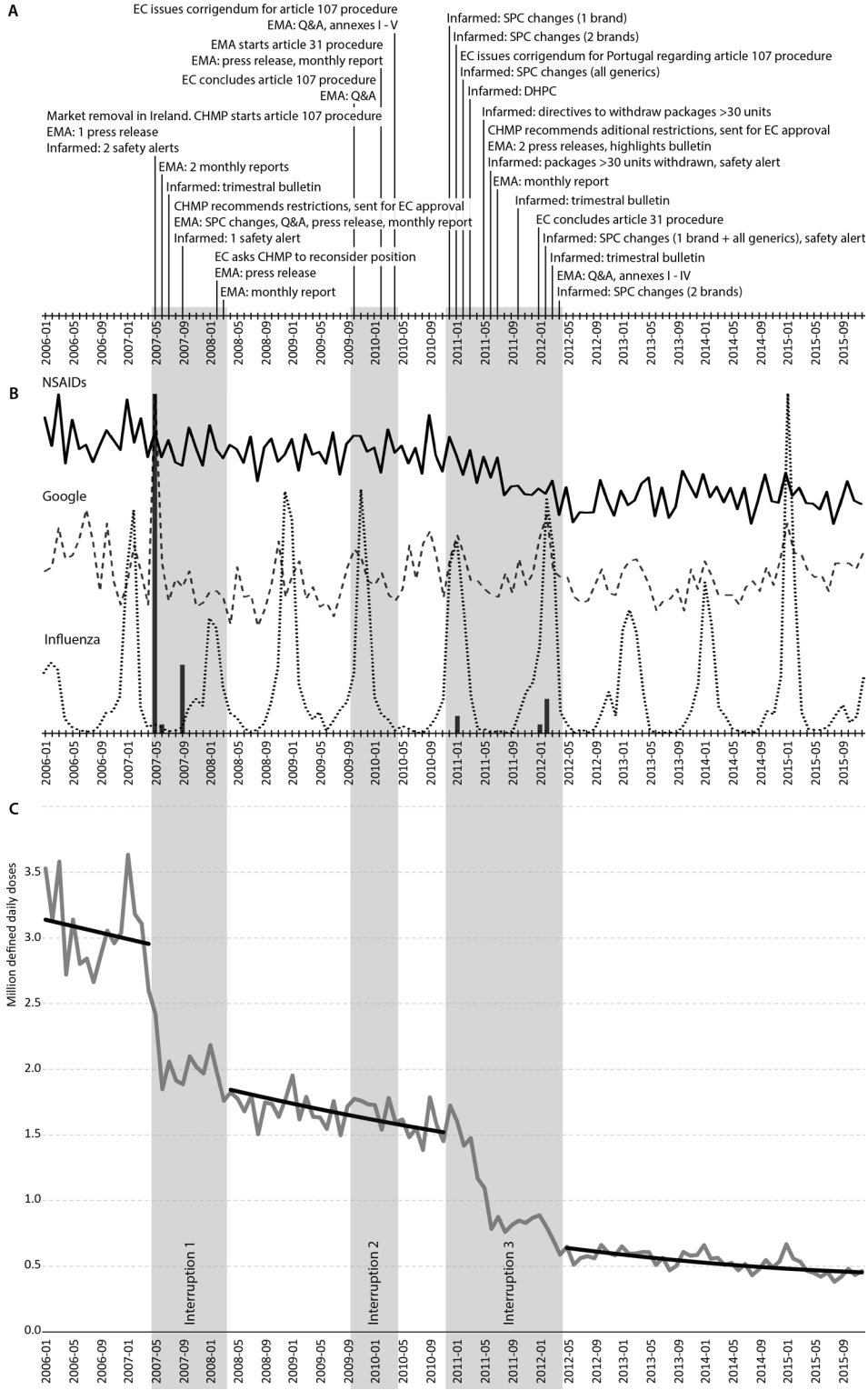
Interruptions

The search in the European Commission, EMA and INFARMED's websites found 46 relevant results, these are summarized in figure 1 - panel A. Concurrent factors are shown in figure 1 – panel B. A detailed description of the events timeline and additional references are given in the supplementary appendix.

Interruption 1 occurred between May 2007 and March 2008. It began with the withdrawal from market in Ireland,[4] which led EMA to initiate an article 107 procedure to review nimesulide safety.[10] This was reported by EMA and Infarmed, frequently in general media and associated with a peak in Google searches. Subsequently, the CHMP recommended restrictions on marketing authorizations for nimesulide, which was again picked up by the media. However, the European Commission did not endorse the recommendations.

Interruption 2 began in October 2009 and ended in April 2010. During this period the European Commission reached a final decision recommending restrictions on nimesulide use, and mandated the CHMP to conduct a wider safety review in an article 31 procedure.[11]

Interruption 3 was the period between December 2010 and April 2012. A corrigendum was issued for Portugal regarding the article 107 decision.[12] Summary of product characteristics and package leaflets were changed, a direct healthcare professional communication was sent, and packages over 30 units were withdrawn in accordance with this decision. Shortly after that, the CHMP announced its opinion regarding the article 31 procedure, which was endorsed by the European Commission.[13] Changes to the summary of product characteristics and package leaflets were implemented in Portugal, but there was no evidence of a second direct healthcare professional communication being sent as recommended by the CHMP.


A
EC issues corrigendum for article 107 procedure
EMA: Q&A, annexes I - V
EMA starts article 31 procedure
EMA: press release, monthly report
EC concludes article 107 procedure
EMA: Q&A
Market removal in Ireland. CHMP starts article 107 procedure
EMA: 1 press release
Infarmed: 2 safety alerts
EMA: 2 monthly reports
Infarmed: trimestral bulletin
CHMP recommends restrictions, sent for EC approval
EMA: SPC changes, Q&A, press release, monthly report
Infarmed: 1 safety alert
EC asks CHMP to reconsider position
EMA: press release
EMA: monthly report
Infarmed: SPC changes (1 brand)
Infarmed: SPC changes (2 brands)
EC issues corrigendum for Portugal regarding article 107 procedure
Infarmed: SPC changes (all generics)
Infarmed: DHPC
Infarmed: directives to withdraw packages >30 units
CHMP recommends aditional restrictions, sent for EC approval
EMA: 2 press releases, highlights bulletin
Infarmed: packages >30 units withdrawn, safety alert
EMA: monthly report
Infarmed: trimestral bulletin
EC concludes article 31 procedure
Infarmed: SPC changes (1 brand + all generics), safety alert
Infarmed: trimestral bulletin
EMA: Q&A, annexes I - IV
Infarmed: SPC changes (2 brands)
2006-01
2006-05
2006-09
2007-01
2007-05
2007-09
2008-01
2008-05
2008-09
2009-01
2009-05
2009-09
2010-01
2010-05
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2012-05
2012-09
2013-01
2013-05
2013-09
2014-01
2014-05
2014-09
2015-01
2015-05
2015-09
B
NSAIDs
Google
Influenza
C
Million defined daily doses
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Interruption 1
Interruption 2
Interruption 3

Figure 1 (oposite) - Timeline of interruptions and global nimesulide use. Panel A: regulatory authorities; CHMP - Committee for Medicinal Products for Human Use, DHPC - Direct Healthcare Professional Communication, EC - European Commission, EMA - European Medicines Agency, INFARMED - Portuguese National Authority of Medicines and Health Products, Q&A - Questions and Answers, SPC - Summary of Product Characteristics. Panel B: cofactors; non-steroidal anti-inflammatory drugs dispensing (solid line), Google trends (dashed line), influenza-like illness (dotted line), and news (dark grey bars). Panel C: nimesulide dispensing in defined daily doses (gray line) with fitted segmented regression model (black line); gaps in the model represent periods when a significant interruption occurred. Vertical light grey bars across panels A to C represent interruption periods.

Total NSAID use, Google trends searches and influenza-like illness activity are shown in figure 1 – panel B. NSAIDs entering or exiting the Portuguese market are shown in the appendix. None met the threshold for a peak market share of at least 5%.

Impact on nimesulide use

The evolution of nimesulide dispensing with the fitted segmented regression model is shown in figure 1 – panel C. The regression model variables are detailed in table 1. At the beginning of the series, nimesulide use was declining. Interruption 1 was associated with a decrease in level and a deceleration in the declining trend.

Table 1 - Segmented regression model for global nimesulide dispensing. Model $R^2 = 0.992$.

Variable	Effect estimate (95% CI)		p value
Intercept	1 157 360.4	(851 947.0, 1 462 773.8)	<0.001
Time since series start*	-12 246.7	(-16 022.9, -8 470.6)	<0.001
Interruption 1†	-824 729.9	(-960 994.1, -688 465.7)	<0.001
Time after interruption 1 squared†	55.5	(24.9, 86.1)	0.001
Interruption 3‡	-449 018.4	(-566 298.1, -331 738.7)	<0.001
Influenza before interruption 3 (cases / 100 000)	1 685.0	(752.8, 2 617.3)	0.001
Total NSAID dispensing (DDD)	0.137	(0.115, 0.158)	<0.001
January	108.621,4	(43 000.2, 174 242.6)	0.001
February	66 263.8	(4 168.5, 128 359.1)	0.037
December	72 937.4	(10 040.1, 135 834.7)	0.024

* January 2006 = 1. † April 2008 = 1. ‡ Mai 2012 = 1. DDD – defined daily doses.

Interruption 2 did not show a significant effect. Interruption 3 was associated with a decrease in level, but no change in trend. Nimesulide dispensing declined from a monthly average of 3.1 million DDD before interruption 1, to 1.6 million from interruption 1 to interruption 3 (-45.3%) and to 0.5 million after interruption 3 (-67.9% than in the previous period). Influenza-like illness incidence showed a positive association with nimesulide prescription before it was introduced as a contra-indication (interruption 3), but not after the changes.

Figure 2 shows the evolution in dispensing of the five oral NSAIDs with the highest market share in 2006 over the study period. The decrease in nimesulide during this period coincided with increased use of etoricoxib, ibuprofen and naproxen, decreased use of diclofenac, and globally decreasing NSAID sales.

Figure 3 shows nimesulide dispensing by prescribing site between 2008 and 2015 and table 2 the respective segmented regression models. All sites showed a trend towards declining nimesulide use after interruption 1 (at the start of the

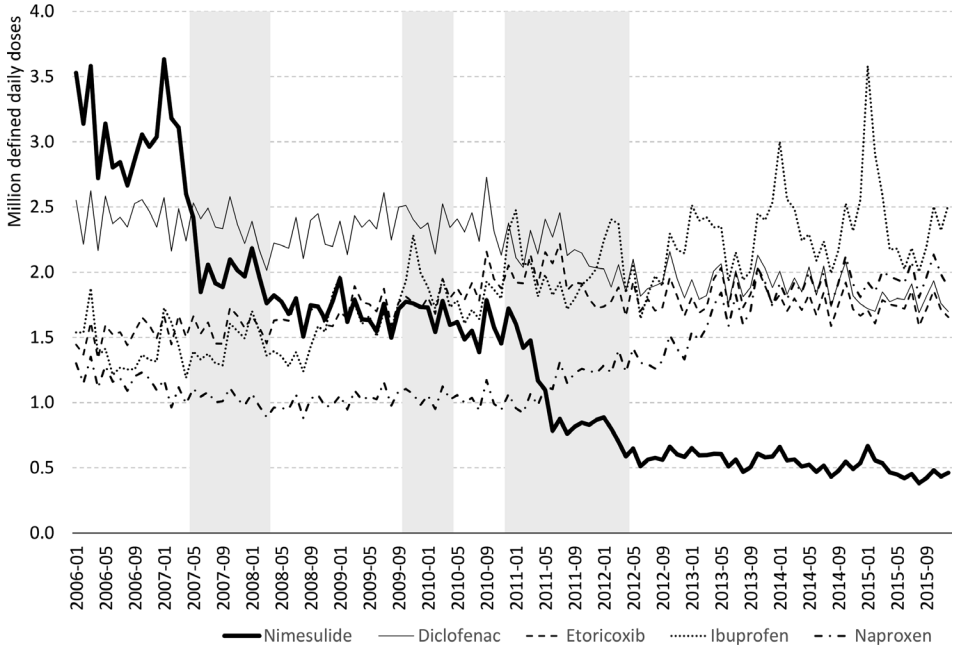
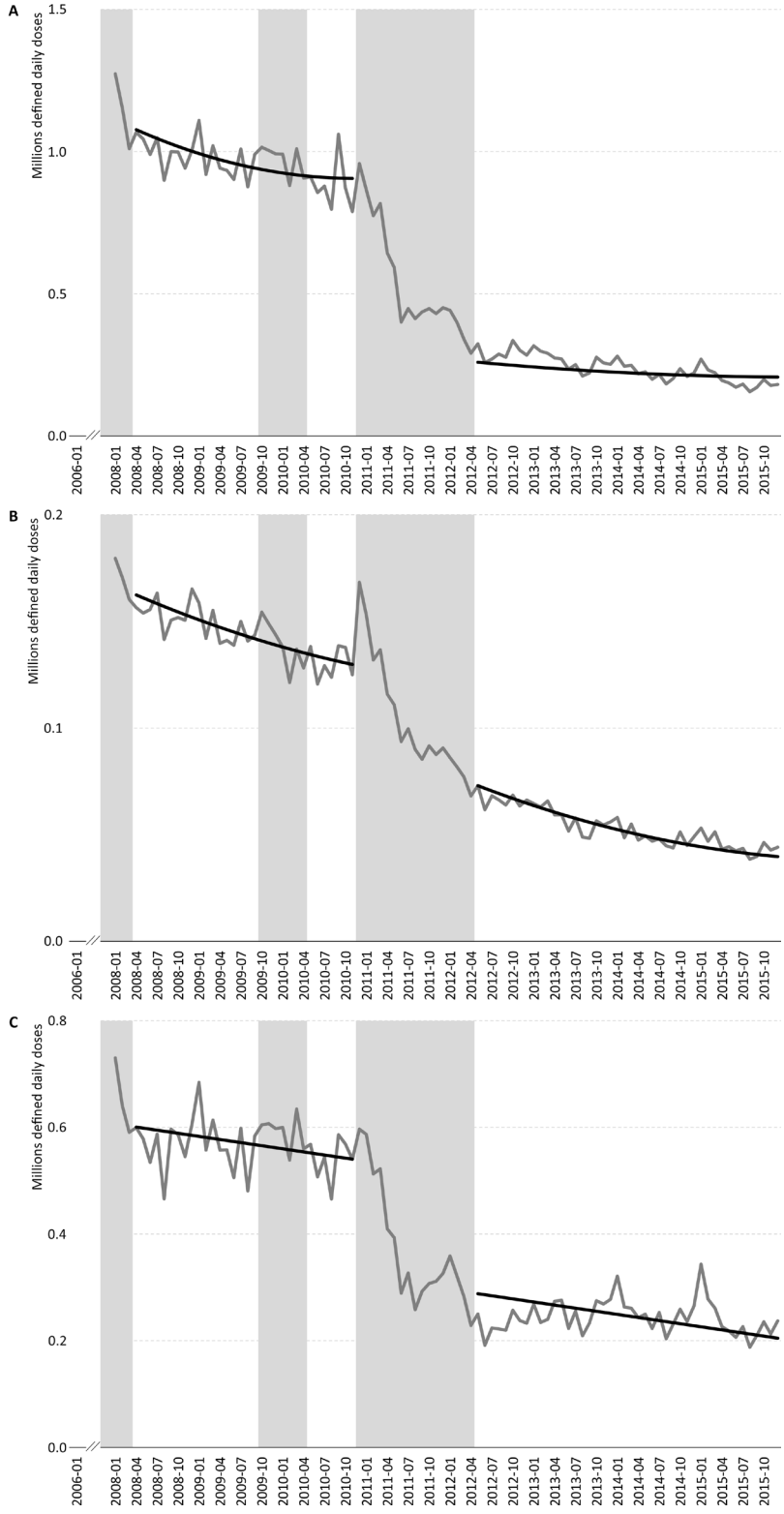


Figure 2 – Dispensing of the five NSAIDs with highest market share in the Portuguese market during the 2006-2015 period. Light grey vertical bars show the interruptions periods.

Figure 3 (oposite) – Nimesulide dispensing by prescribing site category. Panel A – National Health Service primary care. Panel B – National Health Service hospitals. Panel C – Other prescribing sites. All panels show nimesulide dispensing in defined daily doses (gray line) with fitted segmented regression model (black line). Vertical grey bars across panels A to C represent interruption periods.


A
Millions defined daily doses
1.5
1.0
0.5
0.0
B
Millions defined daily doses
0.2
0.1
0.0
C
Millions defined daily doses
0.8
0.6
0.4
0.2
0.0
2006-01
2008-01
2008-04
2008-07
2008-10
2009-01
2009-04
2009-07
2009-10
2010-01
2010-04
2010-07
2010-10
2011-01
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2011-07
2011-10
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2012-04
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2012-10
2013-01
2013-04
2013-07
2013-10
2014-01
2014-04
2014-07
2014-10
2015-01
2015-04
2015-07
2015-10

Table 2 - Segmented regression model for nimesulide dispensing by prescribing site.

Variable	Effect estimate (95% CI)	p value
NHS Primary Care – model R^2=0.996		
Intercept	253 373.6 (156 554.0, 350 193.1)	<0.001
Time after interruption 1*	-11 219.8 (-14 890.0, -7 549.6)	<0.001
Time after interruption 1 squared*	172.4 (70.1, 274.6)	0.001
Interruption 3†	-465 208.0 (-568 833.7, -361 582.2)	<0.001
Time after interruption 3†	-7 958.8 (-14 819.1, -1 098.5)	0.024
Time after interruption 3 squared†	-148.4 (-264.3, -32.6)	0.013
Influenza before interruption 3 (cases/100 000)	747.5 (455.8, 1 039.2)	<0.001
Total NSAID dispensing from NHS primary care (DDD)	0.102 (0.090, 0.115)	<0.001
May	-19 157.2 (-35 945.2, -2 369.3)	0.026
July	-18 648.3 (-35 546.1, -1 750.5)	0.031
October	-35 363.4 (-53 396.7, -17 330.1)	<0.001
November	-27 622.8 -44 659.8, -10 585.9)	0.002
NHS Hospitals – model R2=0.996		
Intercept	86 992.3 (70 194.2, 103 790.4)	<0.001
Time after interruption 1*	-1 418.4 (-1 642.7, -1 194.1)	<0.001
Time after interruption 1 squared*	11.1 (5.6, 16.7)	<0.001
Interruption 3†	-45 989.7 (-51 519.6, -40 459.8)	<0.001
Time after interruption 3†	-946.9 (-1 573.3, -320.5)	0.004
Influenza before interruption 3 (cases/100 000)	115.0 (74.1, 155.8)	<0.001
Influenza after interruption 3 (cases/100 000)	66.2 (30.9, 101.5)	<0.001
Total NSAID dispensing from NHS hospitals (DDD)	0.045 (0.035, 0.055)	<0.001
March	3 246.3 (346.8, 6 145.8)	0.029
October	2 591.5 (28.5, 5 154.5)	0.048
December	2 970.9 (242.0, 5 699.9)	0.033
Other prescribers – model R^2=0.996		
Intercept	338 779.751 (298 372.2, 379 187.3)	<0.001
Time after interruption 1*	-1 939.9 (-2 283.6, -1 596.2)	<0.001
Intervention 3†	-222 969.0 (-241 456.0, -204 481.9)	<0.001
Influenza before indication removed (cases/100 000)	468.5 (316.2, 620.7)	<0.001
Influenza after indication removed (cases/100 000)	232.8 (56.6, 409.0)	0.010
Total NSAID dispensing from other prescribers (DDD)	0.075 (0.062, 0.088)	<0.001
January	26 465.9 (10 241.0, 42 690.8)	0.002
June	-26 059.6 (-37 871.7, -14 247.5)	<0.001
August	-30 255.8 (-43 182.2, -17 329.4)	<0.001

* April 2008 = 1. † May 2012 = 1.

series), albeit decelerating in Portuguese NHS primary care and NHS hospitals. Interruption 2 was not associated with significant changes. Interruption 3 was associated with a level drop across all site categories, and an acceleration of the decline in NHS primary care and NHS hospitals. The average monthly dispensing comparing the period between interruptions 1 and 3 and after interruption 3 declined 75% in NHS primary care, 62.9% in NHS hospitals, 57.1% in other prescribing sites. Influenza-like illness incidence was associated with increased nimesulide use prior to it being introduced as a contraindication in all prescribing site categories. After that, the association continued only in NHS hospitals and other prescribing sites, although the absolute increase was lower than before interruption 3 (table 2).

Nimesulide adverse drug reactions

The number of reported adverse drug reactions per year is shown in figure 4. There was no apparent global trend. Severe hepatic reactions were rare, with two being reported in 2007 and two in 2015.

Discussion

Summary of main results

A high-profile removal from market in one member-state and subsequent complex risk minimization strategies reduced nimesulide dispensing, but did not lead

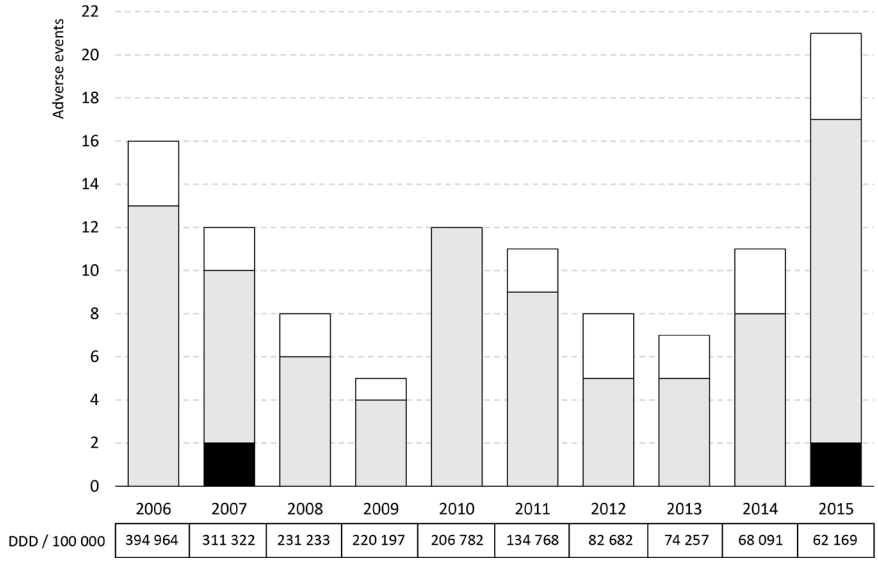

Figure 4 – Number of adverse drug reactions to nimesulide notified per year compared with the number of defined daily doses dispensed per 100.000 population aged 12 years or older. Black: severe hepatic events. Gray: severe non-hepatic events. White: non-severe events.

to any noticeable change in the number of reported adverse events. The number of interventions between 2006 and 2015 and the short intervals between them made it impossible to isolate which components of the risk minimization strategy were most effective.

Interpretation of the results

The largest absolute decline in nimesulide use occurred with interruption 1, when a referral procedure was triggered, generating safety alerts by EMA and INFARMED that were echoed by general media and despite no final decision had been made. Dispensing decreased most between May and June 2007, therefore, we hypothesize that the major driver for the effect of interruption 1 was the high-profile removal from market in Ireland. Media coverage has been shown before to influence patients.[14-16] Since there were no apparent changes in the prescriptions of the other NSAIDs, this strengthens the inference of causality between the high-profile market removal and the reduction in nimesulide dispensing.

Interruption 2 was not associated with significant changes in nimesulide dispensing. As this intervention consisted of actions by the European Commission and EMA not yet implemented in Portugal, it is probable that physicians, pharmacists and the population were unaware of them. This suggests that, to be more effective, EMA's recommendations need to be approved quicker by the European Commission, to have their actions trickling down to member states.

A new drop in level was seen with interruption 3. There was no change in trend globally, but the rate of decline accelerated in NHS primary care and NHS hospitals. Interruption 3 spanned the implementation of restrictions determined by both the first and second review procedures, as measures from the first decision were delayed in Portugal until a corrigendum was issued. The largest decline in nimesulide use happened between March and June 2011, when packages with more than 30 units were withdrawn from market and the direct healthcare professional communication was sent. A smaller decrease was registered between January and April 2012, coinciding with the conclusion of second safety review, national changes in the summary of product characteristics, a safety alert and some media reports. Although mandated in the article 31 decision, we could not find evidence for a second direct healthcare professional communication, which could have reduced the impact of the new restrictions. A systematic review found similar effects of direct healthcare professional communications, black box warnings and public health advisories, but did not present specific results for changes in the number of units per package.[6] Nevertheless, causality between regulatory interventions and nimesulide dispensing is not as strong as in interruption 1, as we also observed changes in the dispensing of other NSAIDs following interruption 3. This suggests that other events could have contributed to changes in the overall

pattern of NSAID prescribing in Portugal. One possibility, is the publication of several articles raising concerns about the cardiovascular safety of NSAIDs. [17]

Interruption 3 was associated with a larger relative reduction in nimesulide use among NHS primary care clinicians than physicians in hospitals and in other prescribing sites (mainly doctors in private practices). NHS primary care was also the only site category where the association with influenza-like illness incidence did not remain significant after it was introduced as a contraindication. This suggests changes in prescribing behavior in line with recommendations were more common among NHS primary care physicians. The possibility that regulatory measures have different results depending on the type of healthcare provider should be further researched.

Contrary to what was expected from the dramatic decline in nimesulide dispensing, there was no reduction in the number of recorded nimesulide adverse events. The number of adverse events per year is small, but it is worrisome that severe hepatic adverse events were not avoided by the decrease in nimesulide use, as shown by the two cases notified in 2015. One possible explanation is an increase in the overall number of adverse event notifications. This was shown to be the case in at least one Portuguese pharmacovigilance unit.[18] It is also possible that increased awareness of the adverse reactions to nimesulide caused more notifications specifically to this drug and masked any reductions associated with decreased use.[19] Decreases in drug use without reduction in clinical adverse outcomes have been documented before,[20] but positive effects have also been observed.[21]

Strengths and limitations

We used an interrupted time-series analysis, one of the most robust study designs when it is not feasible to have a control group.[22,23] We believe that we have high quality data on dispensing since these data are routinely collected for reimbursement purposes. We attempted to assess the clinical impact of the risk minimization strategies by looking at the number of reported adverse drug reactions. We did a thorough search for other events that may have influenced the dispensing of nimesulide and included them in our analysis. Total NSAID dispensing was used to account for historical and instrumentation biases.

There are four main limitations. First, not enough temporal separation existed between events to examine each individually, and there could have been complex interactions between them. Sequential events could have added to, consolidated or decreased the effectiveness of previous events. Second, the small number of severe adverse drug reactions limits conclusions about clinical impact of risk minimization strategies. Third, diagnosis data was not available, which precludes us from knowing if prescribers stopped using nimesulide in patients in whom it was no longer recommended. We attempted to analyze ecological data to infer about use in influenza-like illness, but could not assess other conditions. Finally, our

study is unable to clarify how individual doctors responded to regulatory interventions, as we collected aggregate data. Nimesulide was the sixth highest selling oral NSAID in 2015, which is higher than would be expected for a drug limited to second line. Given the observed increases associated with influenza in NHS hospitals and other prescribing sites, we hypothesize that some physicians are not adhering to the contraindication in patients with fever or flu like symptoms. This merits further research with individually collected data.

Conclusion

Nimesulide use in Portugal decreased significantly after two complex interventions including communication of safety evaluation procedures by regulatory agencies, media coverage, changes to the summary of product characteristics and patient leaflet, withdrawal of large packet sizes, and a direct healthcare professional communication. The decrease was highest for primary care prescribers. However, this was not associated with a decrease in the number of adverse drug reactions reported. Further research is needed to be able to discern the effect of each intervention individually and how contiguous interventions interact to produce changes in drug use.

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Conflict of interest statement

The authors declare they do not have conflicts of interest regarding this manuscript.

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Effect of European Medicines Agency's Regulatory Measures on Nimesulide Utilization in Portugal – Appendix

Timeline of events

When the Irish Medicines Board suspended marketing authorizations for nimesulide in May 2007,[1] EMA started an article 107 procedure to review nimesulide's safety. This was publicly reported by both EMA and INFARMED,[2-4] and in 40 news pieces from 20 media sources. It coincided with a peak in Google searches. In June and July, the procedure was reported in other public documents by EMA[5,6] and INFARMED[7] and in one magazine. In September, the CHMP recommended that marketing authorizations for nimesulide should be restricted. EMA and INFARMED informed health professionals and the public,[8-13] and eight news from five sources were found. However, the European Commission did not endorse the recommendations and asked CHMP to reconsider its opinion in February 2008.[14] This was noted in an EMA press release in March.[15] Thus, the period between May 2007 and March 2008 was considered interruption 1.

In October 2009, the European Commission reached a final decision on the article 107 procedure.[16] The recommended restrictions are detailed in table A1.[17] The CHMP was mandated to conduct a wider review of nimesulide's benefits and risks under an article 31 procedure,[1] which was reported to begin in February 2010.[18,19] The decision on the article 107 procedure had a corrigendum published by the European Commission in March[20] and by EMA in April.[21] Interruption 2 spanned the events from October 2009 to April 2010.

The summary of product characteristics and package leaflets changes in Portugal began in December 2010 and were concluded in March 2011. In January 2011, two news pieces reported on Prescrire's decision to place nimesulide in its avoidance list. In March, the European Commission published a second corrigendum on the article 107 procedure for Portugal.[22] A direct healthcare professional communication was sent also in March.[23] Packages over 30 units or with the previous leaflet version could not be dispensed after June 20 2011.[24] The CHMP issued its opinion on the article 31 referral in June and this was divulged by EMA and INFARMED.[25-27] Nimesulide safety was mentioned by EMA again in July,[28] and by INFARMED in October.[29] The European Commission decided the article 31 procedure in January 2012, endorsing the CHMP's recommendations.[30] Decision details are described in table A1.[31] INFARMED published information regarding this decision in February and March and EMA in April 2012.[32-34] The new restrictions were reported in the news once in January and in four instances in February. Changes to the summary of product characteristics and package leaflets began in February and ended in April 2012. We were unable to find any record of a direct healthcare professional communication sent in Portugal concerning this decision. Interruption 3 was thus defined as the period between December 2010 and April 2012.

Table A1 - Regulatory decisions regarding nimesulide.

Article 107 referral – 16 October 2009[17]
EMA recommendations - The decision to prescribe nimesulide should be based on an assessment of the individual patient's overall risks. - The minimum effective dose should be used for the shortest duration to reduce the undesirable effects. - The maximum duration of a treatment course with nimesulide was limited to 15 days. Therefore, pack sizes above 30 units would be withdrawn and not authorized. - New contraindications: . Concomitant exposure to other potentially hepatotoxic substances; . Alcoholism, drug addiction; . Patients with fever and/or flu-like symptoms. - New special warnings . Patients receiving nimesulide who develop fever and/or flu-like symptoms should discontinue treatment. - Maintenance of the Marketing Authorisations required: . Submission of 6-monthly Periodic Safety Update Reports with a specific overview of hepatic reactions; . Conduct of a pre-clinical study on identification of reactive metabolites and protein adduct information. . Conduct a review of epidemiological data to review the risk of hepatic damage from nimesulide. . Implementation of a retrospective cohort study, followed by a prospective cohort study in transplant centers addressing the relative risk of nimesulide in respect to other NSAIDs to cause severe hepatic reactions; . Update of Risk Management Plan; . Information of healthcare professional via a 'Direct Healthcare Professional Communication' letter; . Evaluate the effectiveness of risk communication on nimesulide; . Perform a survey to clarify the modes of use of nimesulide in selected EU Member States to identify potential misuse. **Additional restrictions by the European Commission** - Limit the prescription of nimesulide to second line treatment; - Introduce a clear obligation upon the marketing authorization holder to inform healthcare professionals of the safety risks associated with this product
Article 31 referral – 23 January 2012[31]
- Nimesulide use should be restricted to acute conditions only (treatment of acute pain and primary dysmenorrhea) - The risk-benefit balance is no longer favorable in symptomatic treatment of painful osteoarthritis, and the indication is to be removed. - Market authorization holders should inform healthcare professionals via a Direct Healthcare Professional Communication.

Sales of non-steroidal anti-inflammatory drugs

Tables A2 and A3 detail changes in the Portuguese NSAID market during the study period.

Table A2 - Non-steroidal anti-inflammatory drugs entering or leaving the Portuguese market between January 2006 and December 2015.

NSAID	Entry	Exit	Peak sales date	Peak sales (thousands DDD)	Peak market share (%)
Lumiracoxib	June 2007	December 2008	August 2007	308.8	2.38
Azapropazone	Before 2006	January 2008	January 2006	78.5	0.52
Sulindac	Before 2006	September 2009	June 2006	12.4	0.09
Niflumic acid	Before 2006	August 2013	October 2008	4.2	0.03
Fenbufen	Before 2006	December 2010	December 2006	2.8	0.02
Tiaprofenic acid	Before 2006	February 2009	January 2006	2.8	0.02
Phenylbutazone	Before 2006	May 2010	January 2006	0.1	0.001

Table A3 – Top 10 NSAIDs in the Portuguese market in 2006 and 2015

Substance	2006 market share (%)	2015 market share (%)	Difference (%)
Nimesulide	21.5	4.2	-17.2
Diclofenac	17.2	15.9	-1.4
Etoricoxib	10.7	15.3	+4.6
Ibuprofen	9.9	21.6	+11.7
Naproxen	8.5	17.4	+8.9
Meloxicam	7.6	3.1	-4.6
Celecoxib	5.3	4.2	-1.1
Piroxicam	4.5	1.5	-2.9
Aceclofenac	3.9	2.9	-0.9
Etodolac	2.1	8.0	+6.0

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Part V – Actively changing prescriber behavior

Manuscript 5: An open cluster-randomized, 18-month trial to compare the effectiveness of educational outreach visits with usual guideline dissemination to improve family physician prescribing – study protocol

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Abstract

Background: The Portuguese National Health Directorate has issued clinical practice guidelines on prescription of anti-inflammatory drugs, acid suppressive therapy, and antiplatelets. However, their effectiveness in changing actual practice is unknown.

Methods: The study will compare the effectiveness of educational outreach visits regarding the improvement of compliance with clinical guidelines in primary care against usual dissemination strategies. A cost-benefit analysis will also be conducted. We will carry out a parallel, open, superiority, randomized trial directed to primary care physicians. Physicians will be recruited and allocated at a cluster-level (primary care unit) by minimization. Data will be analyzed at the physician level. Primary care units will be eligible if they use electronic prescribing and have at least four physicians willing to participate. Physicians in intervention units will be offered individual educational outreach visits (one for each guideline) at their workplace during a six-month period. Physicians in the control group will be offered a single unrelated group training session. Primary outcomes will be the proportion of cyclooxygenase-2 inhibitors prescribed in the anti-inflammatory class, and the proportion of omeprazole in the proton pump inhibitors class at 18 months post-intervention. Prescription data will be collected from the regional

pharmacy claims database. We estimated a sample size of 110 physicians in each group, corresponding to 19 clusters with a mean size of 6 physicians. Outcome collection and data analysis will be blinded to allocation, but due to the nature of the intervention, physicians and detailers cannot be blinded.

Discussion: This trial will attempt to address unresolved issues in the literature, namely, long term persistence of effect, the importance of sequential visits in an outreach program, and cost issues. If successful, this trial may be the cornerstone for deploying large scale educational outreach programs within the Portuguese National Health Service.

Trial registration

ClinicalTrials.gov number NCT01984034.

Keywords

Educational outreach, Academic detailing, Guideline adherence, Family practice, Drug utilization, Program evaluation, Cost-benefit analysis

Background

Patients often do not receive treatment that is supported by best evidence. This includes both failure to provide treatment proven to be cost-effective and provision of care that is unnecessary or harmful [1]. High quality clinical guidelines synthesize the current best knowledge, make transparent recommendations for current best practice, and can improve the quality of care [2]. However, it is recognized that guidelines alone are insufficient to change clinical practice and that implementation strategies are required [3-5].

There is a wide range of such strategies but limited evidence to assess their comparative effectiveness, as there are few head-to-head trials. Some overviews of systematic reviews provide narrative synthesis of the evidence supporting the different interventions [1,4,6,7]. However, primary studies are too diverse and heterogeneous to allow for more robust methods of indirect comparison. The Cochrane Collaboration Effective Practice and Organization of Care Group has assessed several strategies through high quality systematic reviews. Printed educational materials have no apparent effect on processes of care, while educational meetings, educational outreach, local opinion leaders, audit and feedback, computerized reminders, and tailored interventions are associated with small but clinically significant improvements [8-14].

Educational outreach interventions are personal visits by a trained individual (hereafter named as detailer) to health professionals in their own settings [10]. This detailer is usually a healthcare professional (physician, nurse or pharmacist) with special training in communication skills. He or she presents educational contents prepared by an independent organization (such as a university) to an indi-

vidual physician. The Cochrane Review estimates a small but consistent effect on prescription improvement (median 4.8%, interquartile range 3.0% to 6.5%) [10].

Local context

In Portugal, healthcare is provided by two overlapping systems: a publicly funded National Health Service (NHS), and voluntary private and public health insurance. The NHS has universal coverage, and 20% of the population has additional insurance coverage [15]. Thus, most primary care is provided by the NHS.

NHS primary care physicians work in units typically with 4 to 12 doctors, along with nurses and secretaries. On average, each family physician cares for about 1,700 patients. The NHS distinguishes two types of primary care units. The default one is the 'personalized care units' model, in which professionals receive a fixed salary. The other model is the 'family health units', which enjoy greater functional and organizational autonomy [16]. 'Family health units' start as type-A units, in which professionals receive a fixed salary as in the former model. If these A units meet quality indicators targets, they become type-B units, in which health professionals have a mixed payment scheme that includes salary, capitation, and pay for performance.

Within this context, prescription drugs have a variable patient co-payment, depending on their therapeutic value [15]. Electronic prescribing has been mandatory for all NHS reimbursed drugs since 2012. All prescription information is collected centrally by NHS [17].

National prescribing guidelines are commissioned by the National Health Directorate (a government agency) to academic researchers and key opinion leaders. This agency also monitors the quality indicators set in each of its guidelines [18,19]. These guidelines are published in the agency's website (www.dgs.pt). Health professionals are expected to visit this website regularly to keep up-to-date with the latest guidelines. Therefore, this study will not have a group of naive physicians unexposed to guidelines. For this reason, the control group is composed of physicians exposed to passive guideline dissemination (the usual implementation strategy).

Choice of design

The design is a parallel, open, cluster, superiority randomized trial with a 1:1 allocation ratio. This study will assess the effect of educational outreach visits on physician compliance with prescription guidelines. Although the intervention is targeted at individual physicians, there is a risk of contamination if the randomization occurs at the individual level. This is because physicians in the same practice might be influenced by intervention subjects (e.g., by raising awareness of the topics, through discussion of difficult patient cases, or by sharing visit content). Therefore, a cluster-randomized design is appropriate. Also, the costs (e.g., travel expenses, salary costs of the detailers) in a cluster-randomized design will better

approach the real costs of this intervention if implemented as a public health program. Therefore, to minimize contamination and for practical reasons, the unit of allocation will be the primary care unit. The unit of analysis will be the family physician.

Aim and objectives

This trial aims to assess whether educational outreach visits are superior to usual implementation of guidelines regarding the reduction of inappropriate prescribing. The primary outcomes will be the long-term (18 months) effects in the prescription of cyclooxygenase-2 (COX-2) inhibitors, and omeprazole, by family physicians. The secondary outcomes will be the short (1 month) and medium-term (6 months) effects of educational outreach visits in the prescription of these two drug classes. Other secondary endpoints will be the short, medium and long-term effects of educational outreach visits in the prescription of clopidogrel. Finally, the trial will determine the cost-benefit of educational outreach visits.

Methods

The study will be a parallel, cluster-randomized controlled trial comparing educational outreach visits with usual guideline implementation. Besides the standard description below, we also provide a summary of the intervention, a PaT plot, and a cascade diagram in Additional file 1 [20,21]. This protocol was written in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement - Additional file 2.

Participants and setting

The trial will recruit family physicians employed in primary care units of the National Health Service of the Lisbon region, Portugal. This region comprises over 3.5 million patients. A primary care unit (the cluster) will be eligible if it has at least four family physicians (which represent about 6,800 patients). Physicians that are planning to retire within two years, and those without an assigned or still building (far from the average number of patients) patient list will be excluded. At least four family physicians in each unit have to be willing to participate in order for the unit to be included in the trial.

The expected participant flow is described in Figure 1. The research authors will meet with the coordinators of each unit, briefly explaining the protocol and extending them an invitation to participate. The coordinators will be asked to share trial information with other physicians in their units. The researchers will then contact and screen willing primary care units until the target number is met. The enrollment period will last six months. There will be no financial incentive for participation.

Baseline data will be collected from the primary care units (number of family physicians, type of primary care unit, urban versus rural setting, baseline pre-

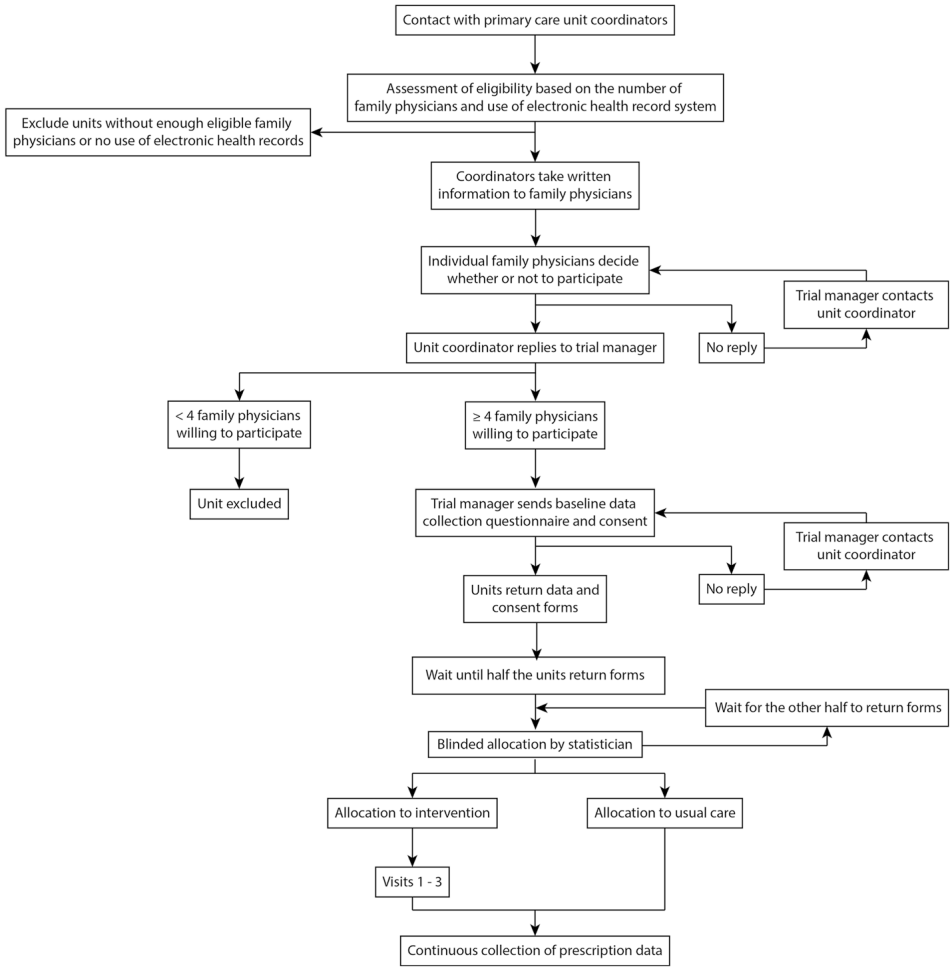

Figure 1 - Flow of participants.

scription of COX-2 inhibitors, baseline prescription of omeprazole) and from the family physicians (age, gender, number of years of practice after vocational training, currently training residents). Participating physicians will agree to schedule three educational outreach visits, one for each guideline.

Allocation to intervention and blinding

Clusters will be enrolled and allocated randomly. To achieve a good balance regarding baseline characteristics that can influence the outcome, the allocation sequence will be determined by minimization [22]. This stratified randomization method will balance the control and intervention groups for number of physicians (4 or 5, 6 or 7, 8 to 12), median baseline prescription of COX-2 inhibitors (above or below the regional median), median baseline prescription of omeprazole (above or below the regional median), proportion of physicians with fewer than 10 years of practice after completing vocational training (above or below

50%), and type of primary care unit (family health unit or personalized care unit). All physicians sending the consent statement before the cluster allocation will be included in the study.

The sequence of intervention visits for each unit will be determined by simple randomization.

Allocation concealment will be ensured by the following procedures: the trial manager (hired and not part of the authors research team) will assign a sequential number to each unit as participation forms are received; only anonymized data about participating units will be sent to the trial statistician (sequential number and minimization variables); data will be sent in two batches, one for each half of all units; the sequence of visits will be determined using the random sequence generator from Random.org (http://www.random.org/sequences/); the statistician will blindly allocate units to each trial arm using minimization and return allocation information to the trial manager.

Due to the nature of the intervention, neither family physicians nor detailers can be blinded. Outcomes are routinely collected by the regional health administration independently of the researchers or the trial and will only be sent to researchers after the intervention has ended. Upon receiving prescription data, the trial manager will generate a random code (using http://www.randomcodegenerator.com) to designate intervention and control units and another code for the order of the visits. Data analysts (the trial statistician plus one of the members of the research team) will receive a file with these codes, ensuring they will be blinded to group and visit sequence allocation until all analyses are completed.

Intervention and comparison

Physicians in units randomized to the intervention will have three educational outreach visits during a six-month period. These visits will promote the implementation of governmental guidelines on the prescription of the following agents: non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors, acid secretion modifiers, and antiplatelets [23-25]. The outcomes for the trial were chosen according to the main key-message from each guideline. For NSAIDs, COX-2 inhibitors should be prescribed only in patients with increased gastrointestinal risk who do not tolerate a classic NSAID associated with a gastroprotective agent; for acid secretion modifiers, all proton pump inhibitors are equivalent in effectiveness, so omeprazole should be used in most patients as it is the least expensive; for antiplatelets, there is no benefit of maintaining long term clopidogrel after a myocardial infarction, acute coronary syndrome, or percutaneous coronary intervention.

During each 15- to 20-minute visit, an academic detailer will promote one of the guidelines to a family doctor (up to three physicians may be present in each visit if they wish to, but one-to-one visits will be preferred and encouraged). The detailer

will also distribute a point of care summary highlighting the main messages. The team of academic detailers will be as following: three members of the steering committee (two family physicians and one academic pharmacologist), three family physicians, and nine family medicine residents in the fourth and final year of their specialty training. The three members of the steering committee completed training in the methodology of academic detailing with the National Resource Center for Academic Detailing (Boston, MA). The other 12 detailers were trained locally by this steering committee, with pretraining study assignments, and 12 hours of face-to-face training that included the principles of academic detailing, role-playing, video-recording and feedback, discussion of the scientific content of each guideline, and knowledge assessment. To ensure consistency, the contents of each visit (structure, guideline features to highlight, and written materials) have been prepared in advance by the steering committee and were used in the training sessions. Whenever possible, a single detailer will perform all three visits to the same physician. The definition and methodology of educational outreach visits has been published elsewhere [10,26].

Usual guideline implementation consists of passive dissemination by their publication on the National Health Directorate's website. Physicians in units randomized to the control group will be offered an unrelated training session (coding with the International Classification of Primary Care, second edition) as a token of good will for participating in the trial.

This trial has a pragmatic purpose. To improve adherence to the educational outreach visits, the Regional Health Administration will allow family physicians to use a patient visit slot (15 to 20 minutes) for each of the three visits, but physicians may also choose to have the visit before or after their regular hours. The first visit will be scheduled by the trial manager contacting the target family physician. Subsequent visits will be scheduled directly between the detailer and the target family physician. Also to improve adherence, participating physicians will be asked to allow us to use their personal phone numbers and emails. We will use these to send them a reminder of the visit two days before it is scheduled. Rescheduling the visit will be allowed up to the day before it is scheduled to take place; if the physician is unable to attend the visit but cannot warn the detailer beforehand, no additional efforts will be made to reschedule that visit (i.e., the program will continue with the next guideline). The intervention will be discontinued at physician request or if the physician changes workplace. Participating physicians will not be prohibited from receiving any other interventions during the trial.

Outcomes

Primary and secondary outcomes

There are two primary outcomes, measured at the physician's level. One is the proportion of COX-2 inhibitors (anatomical therapeutic classification [ATC]

M01AH) prescribed within the entire NSAID class (ATC M01A) in defined daily doses 18 months after the intervention. The other is the proportion of omeprazole (ATC A02BC01) within the entire proton pump inhibitors class (ATC A02BC) in defined daily doses 18 months after the intervention.

There are seven secondary outcomes, also measured at the physician's level: the proportion of COX-2 inhibitors within the NSAID class at one and six months; the proportion of omeprazole within the proton pump inhibitors class at one and six months; and the number of defined daily doses of clopidogrel prescribed per 1,000 registered patients at 1, 6 and 18 months. The proportion of clopidogrel (ATC B01AC04) within the platelet aggregation inhibitors (ATC B01AC) was not selected as an outcome because the most commonly used drug in that class is acetylsalicylic acid (ATC B01AC06). This drug is generally sold over the counter, and no reliable data of its consumption exists.

Timing of outcome collection

Unlike a randomized controlled trial for a drug, we do not expect the intervention to be delivered immediately after allocation. This is because there are a limited number of detailers, and their time for visits is also limited (as they themselves are practicing physicians). Plus, family physicians' availability to receive visits from these detailers is also constrained by their heavy workload. These constraints will prevent us from delivering the intervention to all physicians in a short period (e.g., less than one month). We plan to deliver the full intervention to all physicians in the experimental group over a period of six months. For each guideline, we will seek to visit all the physicians belonging to the same cluster in the shortest time possible, to limit contamination within clusters. This will cause the gap between allocation and intervention dates to vary depending on the participating unit. Thus, if we assess the outcome at a fixed time following randomization, participating units will have different follow-up times after the intervention, and as a result the observed intervention effect will be unreliable. Moreover, since we will have three visits for each physician, there will also be differences in the time of intervention between guidelines. For these reasons, outcomes will be measured from specific intervention dates rather than from the general allocation date. This will provide more reliable data about the efficacy of the intervention.

Using the intervention dates poses a problem for the control group, for whom these do not exist. If we were to measure outcomes from the allocation date, there would be up to a six-month time gap compared with intervention units. In this relatively long interval, other factors influencing prescription of the study drugs could arise (e.g., new research or guidelines being published, changes in drug policy in the Portuguese NHS, seasonal trends of prescription of NSAIDs, etc.). We will address this problem by randomizing the dates from which we measure outcomes for each guideline among control units. This will distribute control units along the intervention period, making them more comparable to the exper-

imental group. This will be done by selecting a random month falling within the first and last months of the visits in the intervention group. The trial statistician will blindly assign a random month for each guideline in every control unit after the final visit in the intervention group is made and before outcomes are collected. Outcomes will be measured using the same monthly prescription data for all physicians within a given cluster.

Cost analysis

Global prescription spending will be defined as the sum of the cost of all drug prescriptions of NSAIDs (ATC M01A), acid suppressive therapy (proton pump inhibitors ATC A02BC and their alternatives: H2-receptor antagonists ATC A02BA, antacids ATC A02A, misoprostol ATC A02BB01, and sucralfate ATC A02BX02), and antiplatelets (ATC B01AC), up to 18 months after the intervention. These costs will be compared with the amount spent training the detailers, preparing and printing educational materials, travel expenses to intervention units, payment of detailers, program coordination, and physician time spent with a detailer rather than with a patient. Costs will be analyzed from the point of view of an educational outreach program rather than from conducting research. Therefore, research related costs (such as researcher time for data collection and analysis) will not be considered. Similarly, the unrelated training session offered to the control units will not be accounted for because it is only intended to improve recruitment and would not be necessary for the implementation of an educational outreach program.

Data collection

Researchers will have access to prescription data through a data monitoring system operated by the Regional Health Administration. Data will be collected and provided by employees from this Administration according to researcher defined specifications. Importantly, researchers will not be directly involved in data collection. This information arrives with a two-month delay from the date the prescription is dispensed. The prescription information contained there can be either for acute conditions – single prescriptions with up to two packages to be dispensed within 30 days; or for chronic usage - three identical prescriptions (up to two packages each) to be dispensed within 6 months. Within the drug classes of this study, only NSAIDs cannot be prescribed for chronic usage. Adverse events cannot be collected in this study because only prescription data is available.

Detailers will record whether the planned visit was effectively accomplished, whether it had the planned duration, the number of physicians (including residents) present, whether the visit was made on patient visit time or off hours, the number of times the detailer had previously visited that physician, and feedback from the physician about the educational materials.

Sample size

The research team has obtained pilot data from all physicians of three primary care units. This data was used to estimate within unit variability and the intra-cluster correlation coefficient (ICC). Data was also gathered for all the units in the Regional Health Administration to estimate the mean prescription and standard deviation for the primary outcomes. The mean proportion of omeprazole dispensed was 54.0% of all PPIs (standard deviation, SD, 10.1%) and the ICC was 0.027. The mean proportion of COX-2 inhibitors dispensed was 20.6% of all oral NSAIDs (SD 7.4%), and the ICC was 0.249. The Cochrane review on educational outreach visits found a median adjusted risk difference for improvement in compliance with desired practice of 5.6% (interquartile range 3.0% to 9.0%) and 4.8% specifically for prescribing (interquartile range 3.0% to 6.5%) in previous trials [10]. Therefore, we chose to calculate our sample size assuming the intervention would lead to a 5% absolute difference in compliance with guidelines between intervention and control units.

If we assume a mean cluster size of six physicians per unit, a 1:1 allocation ratio of controls per intervention unit, an alpha type error of 0.025, and a dropout rate of about 15%, then a sample of 110 physicians in each group will allow for 80% power to demonstrate a 5% absolute increase in the proportion omeprazole and a 5% absolute decrease in COX-2 inhibitors. To recruit the necessary number of physicians, 38 primary care units will be required. STATA 12.0 (STATA Corp, TX, USA) and its sampsi and sampclus commands were used to calculate sample size.

Statistical methods

Physicians will be analyzed according to their randomly allocated group regardless of adherence to the intervention (intention to treat analysis). If physicians transfer to another unit within the health region, we will still be able to monitor their prescriptions. If the transfer is to a different health region (i.e., not Lisbon) we will contact the physician and ask for the missing prescription data. In both cases, prescription of clopidogrel will be adjusted to the new patient list. If a physician retires or we are unable to retrieve data from a physician who moved to a different region, then we will use the last working month's prescription.

Both groups will be compared on primary outcomes using generalized mixed-effects models. The ratio of COX-2 inhibitors to the entire NSAID class and the ratio of omeprazole to the entire proton pump inhibitor class and respective 95% confidence intervals will be calculated. Statistical significance will be assumed for a p-value less than 0.025. STATA 12.0 (STATA Corp, TX, USA) will be used to conduct the analysis.

Data monitoring

Given the nature of the intervention, which poses minimal risks to patients, no data monitoring committee will be established.

Ethical approval

This protocol has been approved by the ethics committee of the Regional Health Administration of Lisbon and Tagus Valley. Family physicians invited to participate will receive written information about the main aspects of the trial, namely which data are being collected and the procedures to ensure the non-identifiability of individual prescriber data. They will sign a written consent for researchers to access their data. The trial will only collect aggregated and non-identifiable patient data. As such, the ethics committee waived patient informed consent.

Trial status

At the time of protocol submission, we have obtained ethical approval and have started to contact eligible primary care units. No primary care unit has been randomized. The trial has been registered in ClinicalTrials.gov (NCT01984034) and ENCePP.eu (http://www.encepp.eu/encepp/viewResource.htm?id=5150).

Discussion

Strengths and limitations

Our pilot data about prescription of NSAIDs, acid-suppressive therapy, and antiplatelet therapy suggests that there is room for improving physicians' prescribing, aligning it with evidence, and potentially leading both to improvements in patient outcomes and cost savings to the Portuguese National Health Service. This paper describes a protocol for a cluster-randomized trial to assess whether educational outreach visits have a long-term (18 months) effect on physician prescriptions. Randomized trials are the gold standard to assess intervention effects, and cluster-randomized trials are an appropriate design when the intervention is an education intervention targeted at healthcare providers [27].

In this trial, it will be impossible to blind physicians and detailers to the intervention. Lack of blinding is expected to overestimate the intervention effects [28,29]. To minimize the effect of this bias, we are using prescription, which is an objective outcome measured independently from the researchers. This outcome also minimizes attrition, since it is possible to continue to assess the prescription behavior even if a physician changes workplace (within the same region).

We have chosen prescription-related outcomes over clinical outcomes. In Portugal, hospital discharge diagnoses (coded through the 9th revision of the International Classification of Diseases) are routinely collected for hospital reimbursement purposes, but are only available after considerable delay. Primary care diagnoses (coded through the 2nd edition of the International Classification of Primary Care) began to be collected in 2007 and are available in the regional database within only one month of registration in the medical record. However, both hospital and primary care diagnoses have not been validated for comprehensiveness and accuracy. Moreover, diagnoses associated with incentives may be record-

ed more often than those without incentives [30,31]. Hence, we have chosen to use prescription patterns as main outcomes. All prescription data in the National Health Service is gathered by the Ministry of Health for pharmacy reimbursement purposes. Data are available for both ordered and dispensed prescriptions. Pilot data from three primary care units showed that only about 60% of the prescribed drugs are actually dispensed. This likely arises from several factors: lack of patient adherence to prescriptions, the inability of physicians to match monthly amounts of different medicines in the same prescription sheet (hence the patient will not fill the entire prescription), and errors in printing and composing prescriptions that are subsequently not handed to the patient nor removed from the electronic medical record. For all these reasons, we opted to use dispensed prescriptions data as primary outcomes rather than ordered prescriptions.

Proton pump inhibitors and antiplatelets may be placed in chronic prescriptions, valid for up to six months. This means that data for these drugs may include prescriptions as old as six months prior to dispensing (and hence up to six months prior to the intervention). This may result in an underestimation of the intervention's effect in secondary outcomes (one and six months, which may still include many lingering old prescriptions). This underestimation will be resolved for the primary outcomes (18 months) because by that time all prescriptions issued prior to the intervention will have been dispensed. However, if the intervention effect decreases over time, prescriptions issued as early as 12 months after the intervention may still be dispensed at 18 months and thus lead to an overestimation of the primary outcomes.

The intervention's effect on physicians may change over time. As the program moves forward, detailers are expected to build a relationship with visited physicians. This may improve the detailer's ability to change the physician's prescribing behavior. On the other hand, the physician's curiosity and willingness to participate may decrease, making him or her less receptive to the intervention. To avoid confounding resulting from the order by which each guideline is presented, we will randomly assign the guideline order for each unit.

We are recruiting family physicians from the three types of primary care units described in the introduction. Preliminary data at the regional level suggests that prescription patterns have greater room for improvement in 'personalized care units' (COX-2 inhibitors market share within NSAIDs is 22.8% in personalized care units vs. 17.8% in family health units; and omeprazole market share within PPIs is 53.1% in personalized care units vs. 55.5% in family health units). However, it is possible that recruitment is stronger in type A and type B 'family care units', since their contracts with the Regional Health Administrations state incentives for participation in research projects and lower drug expenditure. This differential participation may compromise the generalizability of our findings to

the Portuguese NHS, especially if physicians respond differently to educational outreach according to the type of unit in which they practice.

Relationship to other studies and expected contribution of this trial

In 2008, a Cochrane Systematic review concluded that educational outreach visits had a small but consistent effect on improving prescribing behavior, and identified areas for further research, namely: head-to-head comparisons between different educational outreach strategies, process evaluation embedded into trials to assess which components influence the effectiveness of the intervention, inclusion of patient outcomes, measurement of costs and sustained/long term/multiple visits educational efforts [10]. Since its publication, a large number of trials of multifaceted interventions that included educational outreach visits have been published. However, it is not yet clear whether educational outreach has a sustained effect and whether the intervention is cost-effective in a broad range of healthcare systems. The current study is innovative and important internationally as it addresses both these questions. Locally, this trial may show the effectiveness and feasibility of a sustained educational outreach program. If successful, it may be the cornerstone for deploying large-scale programs within the Portuguese NHS. This may range from other types of prescription improvement (e.g., much needed increase of generic market share, which in Portugal is only about half the share of Germany or the US; targeting innovative therapy for appropriate patients) to rational ordering of tests and even adequate screening practices. Ideally, governments and academic centers should be well positioned to apply our findings to a variety of educational outreach programs.

Data sharing

All data is property of the Lisbon Regional Health Administration (Portuguese Ministry of Health). Other researchers wanting to access raw data will need to obtain authorization from this institution before data can be shared.

Competing interests

The authors declare they have no competing interests and no financial or non-financial conflicts of interest.

Authors' contributions

DP and PAC conceived the study. ALP, BH, DSR and IS contributed the study design. ALP, DP, DSR and PAC calculated sample size and planed the statistical analysis. PAC is the grant holder. DP, DSR, IS and PAC contributed to recruitment of participants, training of detailers and preparing educational content. All authors contributed to drafting the manuscript, refinement of the study protocol, and approval of the final manuscript.

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Trial steering committee: Daniel Pinto, Bruno Heleno, David S Rodrigues, Isabel Santos, Pedro A. Caetano.

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Additional files

Additional file 1: An open cluster-randomized, 18 month trial to compare the effectiveness of educational outreach visits with usual guideline dissemination to improve family physician prescribing.

Summary of the interventions:

a	**Trial setup**	
	a1	**Clinical practice guidelines development** Prescribing guideline developed from the cultural adaptation of an existing international guideline, public discussion with medical specialists associations, and endorsement by Governmental Authorities and the Portuguese Medical Association.
	a2	Questionnaire with baseline characteristics of participating units: type of primary care unit, number of physicians, proportion of physicians with less than 10 years of practice.
	a3	Data collection from regional prescription registry: median prescription at baseline for COX-2 inhibitors and omeprazole for each of the primary care units willing to participate.
b	**Usual care: passive guideline dissemination**	
	b1	The three guidelines are published in the website of the National Health Directorate's (governmental authority) website.
	b2	Single group-based training session unrelated to prescription (coding with the International Classification of Primary Care, 2nd Edition)
	b3	For the control group the date for the "start" of intervention will be allocated randomly. These will be selected between the date of the first and last visit in the trial.

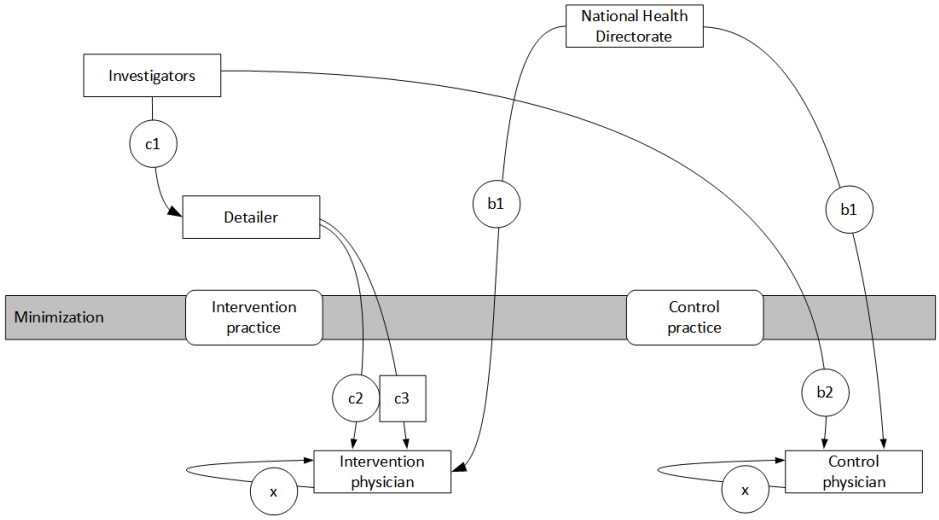
c	**Intervention arm: educational outreach visits** An academically trained detailer will meet with family physicians (FP) in their practices, presenting the key messages of the guidelines and discussing barriers to guideline implementation. Individual visits will be encouraged, but up to three physicians may be present in each visit. There will be a total of three visits (one for each of the three guidelines) each lasting between 15 and 20 minutes. The order of the detailing visits will be randomised for each unit in the intervention arm.	
	c1	Training of academic detailers: Three members of the steering committee (2 FPs and 1 pharmacist) completed training in the methodology of academic detailing with the National Resource Center for Academic Detailing (Boston, MA). The other 12 detailers (3 FPs and 9 FP-trainees) were trained locally by the steering committee, with pre-training study assignments, and 12 hours of face-to-face training which included the principles of academic detailing, role-play, video-recording and feedback, discussion of the scientific content of each guideline, and knowledge assessment. To ensure consistency, the contents of each visit (structure, guideline features to highlight, and written materials) have been prepared in advanced by the steering committee and were used in the training sessions.
	c2	c2(1-3). Academic detailer delivers a detailing session. For each of the three guidelines, there will be a single detailing visit. Whenever possible, a single detailer will perform all visits to the same physician.
	c3	c3(1-3). The detailer will also distribute a point of care summary highlighting the main messages.
x	Interaction between physicians reinforce the intervention within a practice	
d	**Outcome collection** l. Regional prescription registry extraction: COX-2 and NSAIDs prescription data will be collected at 1 month(d1), 6 months (d2) and 18 months (d3) after the respective educational visit has been performed (intervention group) or the equivalent randomly assigned visit date (control group).	

Timing of interventions and assessments (PaT plot)[i]

Time line	Educational outreach visit	Usual guideline dissemination
2-6 months pre-randomisation	a1 a2 a3 b1 c1	a1 a2 a3 b1
Allocation (minimization)		
During 6 months ($0 \leq t \leq 6$)	b1 c2.1 c3.1 x b1 c2.2 c3.2 x b1 c2.3 c3.3 x	b1 b2 x
1 month post-intervention ($1 \leq t \leq 7$)	b1 d1	b1 b3 d1
6 months post-intervention ($6 \leq t \leq 12$)	b1 d2	b1 d2
18 months post-intervention ($24 \leq t \leq 30$)	b1 d3	b1 d3

i Perera R, Heneghan C, Yudkin P: Graphical method for depicting randomised trials of complex interventions. BMJ 2007, 334:127–129.

Plan for the delivery of the intervention (Cascade diagram)[ii]



Additional file 2: Table S1. CONSORT 2010 checklist of information to include when reporting a cluster randomised trial. Table S2. Extension of CONSORT for abstracts 1, 2 to reports of cluster randomised trials.

Not included in the thesis. Available from:

https://static-content.springer.com/esm/art%3A10.1186%2F1748-5908-9-10/MediaObjects/13012_2013_845_MOESM2_ESM.pdf (short URL: goo.gl/TMK4eY)

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Manuscript 6: Educational outreach visits to improve prescription quality: process evaluation of the TEP cluster-randomized controlled trial

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Abstract

Background

Educational outreach visits are complex interventions where educational content is delivered to improve a health professional's behavior. The Trial to Assess the Effectiveness of Educational Outreach in Prescription Guidelines (TEP) was aimed at improving prescribing patterns in primary care. We conducted a process evaluation to analyze TEP´s implementation regarding reach, dose, fidelity, acceptability and perceived impact (the intervention's effectiveness will be reported elsewhere).

Methods

During the pre-intervention stage, data on recruitment of physicians and detailers was recorded by the trial study coordinator. During the intervention, detailers recorded how each visit was delivered and perceived by filling an online visit tracker. After the interventional stage, all detailers were invited to a focus group to share their views on how the intervention was implemented and to gather questions for subsequent physicians´ interviews. Five participating physicians were interviewed by a trained psychologist to gather qualitative data on their views about the intervention. Interviews were used to create a questionnaire, which was sent to all physicians participating in the intervention arm.

Results

The target 38 units (239 physicians) were recruited in a 10-month period, with higher participation of family health units than personalized care units (36.5% vs 2.2% of invited units). Overall visit success rate was 89.4%, with the full educational content being delivered in 97.8% of visits. The physician survey had a 68% response rate, with 98% of physicians considering visits useful to their practice, 96% wishing visits would continue and 96% stating they would recommend the program to other physicians. Five of the twelve active detailers participated in

the focus group, all were pleased to have participated in the trial and would like to continue their activity as detailers in the future alongside their jobs as family physicians.

Conclusions

Process evaluation for the TEP trial showed reasonable reach, high dose and very high fidelity for the implementation of the planned intervention. Acceptability was very high among both participating physicians and detailers. Perceived impact was moderate among physicians and low among detailers. Overall, the trial was successfully implemented.

Trial registration

ClinicalTrials.gov NCT01984034.

ENCEPP: http://encepp.eu/encepp/viewResource.htm?id=6992

Keywords

Educational outreach; Academic detailing; Guideline adherence; Family practice; Drug utilization; Process evaluation; Implementation.

Background

Educational outreach visits (also known as academic detailing) are aimed at changing healthcare professionals' behavior by delivering educational content in face-to-face visits performed by trained persons (usually another health professional).[1] A Cochrane review of available literature found there are currently several ways of conducting educational outreach visits, as some of the components originally described have been altered by different researchers.[2] Although these variations are expected in complex interventions, they may have an impact on the effectiveness of outreach visits to change behavior. Moreover, complex interventions, such as educational outreach visits, may sometimes fail to be fully implemented in randomized trials, or be implemented in different ways in separate trial locations. There could also be contextual factors that lead to variable effectiveness in different subgroups.[3] Consequently, the review's authors conclude that research is needed to understand the sources of variability in effectiveness.[2] Thus they recommend that process evaluations should be embedded into educational outreach trials.

Process evaluations focus on the delivery of the intervention, and may help to interpret the trial's results. Fidelity (the delivery of the intervention as planned), dose (how much of the intervention was actually implemented), reach (if the target audience came in contact with the intervention), acceptability (if the intervention generates resistance) and mechanisms of impact (how does the delivered intervention produce change) should be evaluated in complex interventions to better understand their effects.[3] Process evaluations can thus shed light on how

the intervention was implemented, evaluate separate components of the intervention, how participants viewed the intervention, describe local and contextual factors that may influence the outcome, and identify subgroups where the effect may vary.[4]

The Trial to Assess the Effectiveness of Educational Outreach in Prescription Guidelines (TEP trial) is a cluster-randomized trial to compare the effectiveness of educational outreach visits with that of usual guideline dissemination aimed at improving family physician prescribing.[5] We conducted a process evaluation of the TEP trial to analyze the implementation of the intervention regarding reach, dose, fidelity, acceptability of different components of the intervention and perceived impact.

Methods

In this section, we first provide a summary of the TEP trial protocol, and then detail how the process evaluation was conducted (with data collected before, during and after the intervention stage). The TEP trial has been approved by the ethics committees of the Lisbon and Tagus Valley Regional Health Administration and NOVA Medical School. Physicians were required to give informed consent to participate in the trial.

Setting

In Portugal, primary care services are provided mainly by the government-run National Health Service. Health center groups provide care to a local population and consist of several units with 4 to 12 physicians, who are each responsible for about 1700 patients. Nurses and secretaries work alongside physicians in these primary care units, while psychologists, physiotherapists and other healthcare professionals are shared among units within a health center group. Most physicians work for a fixed salary in personalized care units, but since 2006 they can volunteer to work in family health units, with greater functional and organizational autonomy, and working in a mixed payment system (salary, capitation, fee for service and pay for performance).[6]

Intervention in the TEP trial

The trial protocol for the intervention has been published in detail elsewhere.[5] In summary, family physicians working in primary care units in the Portuguese National Health Service in the Lisbon region were recruited to participate in a parallel, open cluster-randomized trial comparing educational outreach visits with usual guideline implementation. The intervention arm received three educational outreach visits on non-steroidal anti-inflammatory drugs (NSAIDs), acid secretion modifiers, and antiplatelets guidelines published by the Portuguese National Health Directorate.[7-9] Four of the investigators (BH, DP, IS, and PAC) are also authors of these guidelines. Three investigators, two of them family physicians (DP,

DR) and one academic pharmacologist (PAC), received training in educational outreach and then acted as trainers for other detailers.[10] These additional detailers were invited from a pool of family physicians and family medicine residents based upon the investigators' knowledge about personal characteristics and geographic convenience. Detailers were trained to conduct each visit in several stages: introduction, assessing the physician's educational needs, describing features and benefits of the guideline, handling objections, summarizing, obtaining a commitment for prescribing according to a particular key-message in the guideline, and scheduling the next visit. The three researchers and the additionally trained academic detailers performed one on one visits to family physicians (up to three physicians were allowed to be present in a single visit if they requested), which were planned to last for 15 minutes. In each visit a brochure was used by the detailer as visual aid and a small handout was given to the physician as a summary highlighting the main points of the guideline. The order of the visits was randomized to prevent a possible effect of the detailer-physician relationship on effectiveness if the sequence of visits was the same among all participants. Usual implementation in the control arm consisted of passive guideline dissemination by publication on the National Health Directorate's website. To improve recruitment, we offered units in the control arm an optional training session on using the International Classification of Primary Care (ICPC), second edition. We planned the enrollment of 38 primary care units (clusters) with an average of 6 physicians per unit.

Monitoring implementation during the intervention

Before the intervention began, data on family health units and detailer recruitment was recorded by the trial study coordinator as recruitment progressed. An online tool (visit tracker) was developed to help detailers plan and track their visits and to allow investigators to monitor visit progress. It also included questions regarding each visit that detailers would fill out. To avoid inaccuracy in recording data, they were also given a paper version of the questions, which could be used on-site and then transposed to the web version at a later time. During the intervention detailers collected data on the visit's characteristics (location, scheduled and actual time, length, number of physicians present, and interruptions), delivery of the educational program as planned, barriers to change mentioned by the physician, physician interest and commitment to change, adequacy of educational materials, difficulties felt by the detailer, and overall detailer satisfaction with the visit. A successful visit was defined as an interaction between a detailer and one or more physicians where educational content was delivered.

Detailers' perceptions and experience after the intervention

Three months after the last educational outreach visit we conducted a focus group discussion with active detailers. This was facilitated by a trained psychologist. Detailers were asked about their perceptions on the usefulness of academic

detailing, the clinical value of their visits for physicians, their feelings about conducting the visits (namely, approaching participating physicians and the usefulness of each task within the visit), the adequacy of training before the visits and educational materials provided to physicians, personal styles of conducting visits, their perceived influence on physician's prescribing behavior, and if payment was appropriate for their task and time. Input from the focus group was used to plan physician interviews and a first draft of the physician questionnaire. Detailers not able to participate in the focus group were invited to comment by email.

Physicians' perceptions and experience after the intervention

An organizational psychologist conducted individual semi-structured interviews to five participant physicians. The main goal of the interviews was to identify which intervention elements worked well and resulted in behavior change, as well as those that were perceived as not being useful, their willingness to continue to receive educational outreach visits and their views on how well detailers performed. The interviews were transcribed and subjected to content analysis. Based on the interviews' content a questionnaire was developed and tested with four physicians not involved in the trial and slight modifications were introduced to improve readability. The questionnaire had 31 statements to be answered in a six item Likert scale (completely disagree, disagree, partially disagree, partially agree, agree, and completely agree), and also an open text comment section. Answers were categorized as agree or disagree. The questionnaire was sent to all physicians in the intervention arm nine months after the last visit, along with a prepaid response envelope. Physicians could also opt to fill the questionnaire online. To improve response rates, physicians were told they would receive a study participation certificate upon completion of the questionnaire. One week after the questionnaires had been posted, a reminder email was sent to all unit coordinators. Three weeks after the questionnaires had been posted individual email reminders were sent to physicians who had not answered.

Results

We successfully recorded recruitment of family health units and detailers, detailers entered information regarding all visits in the visit tracker, conducted a focus group with five of the twelve active detailers, interviewed five physicians and received 82 questionnaires from physicians in the intervention group (68% response rate).

Reach

Recruitment of primary care units and physicians

Recruitment of participants for the trial began on March 27, 2013. The study was presented to unit coordinators in 13 out of the 15 health center groups in the Lisbon region (the other two were not contacted as they were the most distant

from Lisbon). We were able to recruit the target 38 units out of the 233 health units in these health center groups (16.3%), not all of which would have been eligible, as some had fewer than the specified minimum of four physicians. Within these units, 239 physicians agreed to participate. The mean cluster size was 6.3 physicians per unit, slightly higher than had been anticipated (6.0). The first unit completed study entry procedures in April 2013 and the last in January 2014, hence recruitment lasted 10 months.

Recruitment was higher among family health units than among personalized health care units: 36.5% (35 of 96) vs 2.2% (3 of 137), p<0.001. Units that volunteered to participate had better prescription patterns in NSAIDs and acid secretion modifiers than the regional average when we collected data prior to the trial for minimization purposes. The regional cyclooxygenase-2 (COX-2) inhibitors market share (in defined daily doses) in the oral NSAIDs class was 20.6% (standard deviation ±7.41), while it was 17.9% (SD ±6.39) in participating units (lower better) - p=0.028. Omeprazole market share in the proton pump inhibitors class was 54.0% (SD ±10.09) in the region and 56.4% (SD ±9.52) in participating units (higher better) - p=0.170.

Nineteen units were allocated to each arm, with 120 physicians assigned to the intervention arm and 119 physicians to control (Table 1).

Recruitment of detailers

Of the 22 physicians invited, 17 accepted to be trained as detailers, and 13 completed training. From these, nine performed at least one visit during the study. Six of these were specialists in family medicine, and three were in their final family medicine residency year. The mean age of the nine detailers was 31.5 years old. The remaining four out of the 13 detailers who had completed training did not make visits as they were no longer available when visits begun due to other professional obligations.

Dose

Visits success rate

The overall visit success rate was 89.4%, with 322 visits accomplished out of 360 planned - table 2. Twenty-six visits were attempted but the physician was absent (21) or unavailable (5). Twelve visits were not attempted: two physicians had none of the three visits (one was on maternity leave and the other on extended sick leave); one physician did not wish to receive further visits after an unsuccessful first attempt; and four physicians did not received one of the visits (two because the detailer was unavailable, one was on compassionate leave and the other on sick leave). Each detailer attempted between 6 and 53 visits, median 28.5 visits per detailer. The nine recruited detailers made 66.7% of the visits (successful or attempted) and the three investigators acting as detailers made the remaining 33.3%. All three visits were made by the same detailer in 88.3% of physicians. In 5

Table 1 - Characteristics of participating physicians at the time of randomization.

Characteristic	Intervention (n = 120)	Control (n = 119)
Female - %	70.8	79.0
Age - years, median (P_{25}-P_{75})	52 (41-59)	47 (38-59)
Years in practice, median (P_{25}-P_{75})	13 (6.5-28)	11 (4-28)
Training - %		
Family medicine residency	44.5	47.6
On the job vocational training	24.5	28.6
General practitioner	30.9	23.8
Residency tutor - %	55.8	52.9
Patient list size - n, median (P_{25}-P_{75})	1874 (1812-1923)	1813 (1746-1872)
Unit type - %		
Family health unit	89.2	95.8
Personalized care unit	10.8*	4.2

SD - standard deviation. * After randomization, two personalized care units with 13 participating physicians changed their organization to family health units, therefore, when visits were made 0% of physicians in the intervention group.

units a single detailer made all the visits; in 13 there were two detailers assigned; and in one unit three detailers made visits.

Optional session in the control arm

Eleven units accepted the optional session on ICPC, three chose not to receive it and the other five did not reply to our invitation.

Fidelity

Preparing educational content

The chosen guidelines were summarized by the investigators. Key clinical messages were identified by consensus and used to prepare mock visits to guide detailers training sessions, handouts and color brochures. Brochures used figures and tables to support the discussion during the visit, and handouts listed key messages in plain text or tables and were meant to be used as a desk reference. Draft versions of both were discussed among the investigators and then presented to detailers during their training sessions. Detailer feedback was used to improve content and visual presentation and the final version of visits and educational materials was approved by both investigators and detailers. These materials are available (in Portuguese) from the investigators upon request.

Table 2 - Summary of visits.

Visit outcome - visits, n (%), n=360	
Successful	322 (89.4)
Physician absent	21 (5.8)
Physician unavailable	5 (1.4)
Visit not attempted	12 (3.3)
Target physicians per successful visit - visits, n (%), n=322	
1	287 (89.1)
2	23 (7.1)
3	11 (3.4)
4	1 (0.3)
Successful visits per physician - physicians, n (%), n=120	
0	3 (2.5)
1	6 (5.0)
2	17 (14.2)
3	94 (78.3)
Different detailers per physician - physicians, n (%), n=120	
1	107 (89.2)
2	13 (10.8)
Visits per detailer - visits, median (P_{25}-P_{75})	28.5 (24.8 - 34.0)

Training of detailers

Detailers received course materials in advance and then participated in three training sessions with a total of 12 hours. The first session (3.5h) discussed the theory and components of educational outreach visits, and detailers practiced the opening stages of a visit. In the second session (6h), detailers practiced visits with each other using the three trial guidelines. The third session (2.5h) was used to answer questions about educational outreach visits and the guidelines. All training visits were video recorded and made available to detailers. An online support group was available to detailers throughout the trial, allowing questions about guidelines to be placed to their authors. In the focus group detailers mentioned not having enough time to read all materials sent before the first training session due to their daily activities as physicians. This led to an initial difficulty interpreting the guidelines during the first training session. However, they overcame

the difficulty in the following sessions. Being able to watch video recordings of practice visits made by every detailer was considered very useful, as it allowed detailers to analyze their technique and compare themselves with others.

Delivering educational content

The full educational content was delivered in 97.8% of visits. In the remaining visits, the most common reason for not delivering the full content was physician lack of time for a full visit. Detailers followed all planned stages of the visit in 89.4% of visits. The introduction stage was missed in 0.9% of visits, needs assessment in 4.3%, features and benefits in 10.6%, handling objections in 0.9%, summarizing in 1.6%, obtaining a commitment in 7.5% and scheduling the next visit in 0.3%.

Detailers reported feeling difficulties in their role in 11.5% of visits, the most common difficulties were: physicians claiming that they already followed the guideline, not enough time for the visit, not being able to obtain a prescribing commitment, and uncertainty when dealing with scientific questions. Overall, detailers reported being pleased or very pleased with their role in 93.8% of visits.

In the focus group, detailers mentioned that many physicians claimed to be already following the guideline, and therefore they would not need to change their behavior substantially. However, detailers felt there was still room for improvement, which was not recognized by physicians. These views were consistent with the physician survey, where 91% of physicians agreed they were already practicing what the National Health Directorate's guidelines recommended, but 63% mentioned they often didn't have enough time in a patient visit to follow these guidelines. For detailers, this argument of already following guidelines made their request for a commitment to change prescribing behavior more difficult. Detailers reported feeling more comfortable informing physicians about the guideline than asking for commitments to prescribing changes. After completing the visits, detailers mentioned that training had focused mainly on the scientific content of guidelines, partly because this was where they were more engaged. They considered that the scientific debate during the visits was the easiest part (unlike what they expected), attributing this to their training as physicians. In contrast, obtaining a commitment to change prescribing behavior at the end of the visit was highlighted as the hardest part of the visit. These difficulties were attributed to lack of training, but also to detailers not being comfortable with asking for a prescribing commitment. In the focus group, some detailers questioned whether asking for a prescribing commitment changed the effectiveness of the intervention or it could be dispensed with. Their concern was that this could damage the empathy they had built with the physician in the first part of the visit.

Protocol deviations

During the trial, nine minor protocol deviations were recorded. Seven of these were changes in the planned order of the visits involving eleven physicians. In four

units the incorrect visit was mistakenly performed by the detailer; in two units the physician or the detailer were unable to schedule the visit in the appropriate month; and in one unit a pregnant physician asked to receive the final visit one week before the planned schedule as she would be on maternity leave. Another minor deviation occurred in one unit where two physicians did not receive the final visit due to unforeseen unavailability by both the assigned detailer and later the replacement detailer designated by the steering committee. The final minor deviation occurred when a detailer accepted to perform a visit to four physicians at once at their request, disrespecting the maximum allowed of three physicians at once in a single visit.

Acceptability

Scheduling visits

In the focus group detailers mentioned that in some places scheduling visits was difficult at first, as some physicians did not recall having volunteered for the study and some office secretaries blocked the access to physicians. After the first visit had been made, however, access to those hard-to-reach physicians usually improved considerably. At other units, the role of office secretaries in providing access to physicians was praised by detailers. Detailers mentioned that respecting the rules of each unit they visited and not asking for special privileges was helpful when dealing with office staff. They also considered it would have been better if secretaries were informed of the study beforehand (instead of just the physicians). Scheduling was easier when detailers already professionally knew the physician before the study. Sometimes detailers stayed in the waiting room until the physician was available, while in other units they were invited in to wait in the inside corridor or a meeting room. Detailers felt that an official identification badge was not needed. Sending a reminder on the day before the visit, arriving early, and notifying the physician they had arrived by text message were seen as facilitators. Some physicians also helped by walking the detailer to the next colleague's office after the visit. Detailers felt frustrated when some physicians left the practice despite having scheduled a visit.

Physicians per visit

In 89.1% of successful visits only the target physician was present, in 7.1% there were two target physicians, three in 3.4%, and four in one visit. All visits with more than one target physician happened at the doctors' request. One or two family medicine residents or medical students were present in 22.4% of visits.

Detailers in the focus group reported that when physicians asked to receive the visit in groups of two or three they were more interactive, asking more questions and ending the visit more convinced of the need to change. This was also thought to be the case, albeit to a lesser extent, when a physician was visited with one or more residents present. The detailers' perceptions are consistent with the phy-

sician survey, where 33% of physicians disagreed with the statement that they preferred individual visits.

Timing and location of visits

Physicians choose to receive detailers between patient appointments in 55.6% of visits and before or after seeing their patients in the remaining 44.4%. Nineteen percent of visits were scheduled between 8 a.m. and 12 p.m., 68.4% between 12 and 5 p.m., and 12.6% between 5 and 8 p.m. Detailers reported 58.7% of visits began on time, 29.8% were late (median 15 minutes, interquartile range 15-30 minutes) and 11.5% were early (median 15 minutes, interquartile range 15-30 minutes). The length of the visits was the planned 15 minutes in 75.5%, shorter in 13.0% (median 9.5 minutes shorter, interquartile range 5-10 minutes) and longer in 11.5% (median 10.0 minutes longer, interquartile range 5-18 minutes).

In the focus group, detailers mentioned it would be useful to have instructions on how long to wait when a physician was delayed. Detailers noted that shorter visits happened when the physician informed them he/she was pressed with time. Some physicians were described by detailers as disorganized, having not set aside enough time for the visit. Longer visits occurred when physicians showed interest in debating the guideline.

In the physician survey, 91% agreed that 15 to 20 minutes was the ideal duration for visits, and 18% said visits had cause some disruption of their schedule for that day.

Most visits were held in the physician's office (86.3%), 8.1% in the unit's meeting room, 2.5% in another physician's office and 3.1% in other locations. There were interruptions in 24.2% of visits, 93.6% of which were considered by the detailer to cause none or little disturbance.

In the focus group detailers said they were indifferent about the location where the visit was held, but felt physicians were more comfortable in their own office. They also noted that the visit was more likely to be interrupted if it was conducted in the physician's office. This was consistent with data entered in the visit tracker, where 26.6% of visits in the physician's own office were interrupted compared with 9.1% of visits held elsewhere, odds ratio 3.6, 95% confidence interval 1.2-14.4, p=0.001.

Barriers to change

Patient resistance to changing the usual prescription (28.3% of successful visits) and changing a prescription decided by another physician (26.7%) were the most common barriers to change recorded by detailers. Not knowing the guideline (13.4%), disagreeing with the guideline (5.0%), hospital specialists not following the guideline (4.3%) and lack of time (3.4%) were also common barriers identified during visits.

Patients were willing to change their medications according to 80% of physicians, and 83% considered patients were willing to change medications initiated by other physicians. When questioned about their sources of information about prescribing medicines, 87% of physicians identified the National Health Directorate's guidelines, 98% consulted a colleague in the same unit, and 51% consulted a hospital specialist in that area.

Brochures and handouts

In 98.8% of the visits detailers considered the educational materials as adequate to answer all of the physician's questions, and rated 90.4% of physicians as interested or very interested in the handout.

In the focus group, detailers rated physician's reactions to the materials used in the visit as very positive. The large color brochure was considered very helpful as a visual aid, both for the detailer's organization of the visit and for helping the physician understand the guideline's content. The small handout guideline summary was considered very practical as a point of care aid in daily practice. Detailers mentioned some physicians kept all three handouts at hand in a specific folder on the desk or the bookshelf. In a few units, physicians requested electronic versions to be made available on physician's desktops. Some physicians asked for the large brochure, but most felt the handout was enough.

In the questionnaire, 98% of physicians agreed that brochures were useful in explaining the visit's educational content, and 96% found the handouts useful in clinical practice. 79% of physicians wanted future visits to include patient handouts.

Detailers

Detailers felt most physicians had enjoyed their work and had found the visits useful. Younger detailers felt their age was not a problem and even had a positive impact. Participating in the trial was seen by detailers as allowing them to gain detailed knowledge of the three guidelines in the trial, update medical knowledge in general, improve their own practice as physicians and critical reading skills, get to know other units, change their daily routine as physicians with a different kind of activity, and be useful to other family physicians. Payment was considered adequate, but not as important as the opportunity to be part of a project seen as innovative, important, and with potential gains for patients and physicians.

As for continuing as detailers in the future, all in the focus group showed interest if it could be made alongside their regular activities as family physicians, and some would consider decreasing their weekly schedule as physicians to be able to make more visits as detailers. None wanted to stop clinical practice to become a full-time detailer.

In the physician survey, 99% agreed that detailers had good knowledge about guidelines and good communication skills, 93% agreed they had practical expe-

rience applying guidelines to real patients, 96% agreed they were able to answer the questions physicians posed about the guideline being presented, and 80% disagreed with the statement that detailers were more committed with economic savings than clinical benefits. For future visits, 79% of physicians disagreed that they would rather be visited by more experienced physicians, 78% agreed they would gladly accept visits by family medicine residents, and 76% disagreed they would find the visits equally useful if performed by other health professionals that were not physicians.

Perceived impact

Physician immediate reactions

Detailers classified 93.5% of visits as having an interested to the physician, 4.3% as indifferent, and 2.2% as skeptic. In the focus group detailers consider the vast majority of physicians as very receptive, with a minority described as nodding without really engaging.

Perception of utility

Detailers recorded that physicians committed to changing their prescribing behavior in 84.5% of visits. However, in the focus group detailers mentioned they had perceived visit effectiveness as small. They felt that physicians who showed most interest and engagement during the visits were the ones who most often claimed to be already following the guidelines. Detailers expected some changes to occur, especially in younger physicians. Older physicians were seen as being less receptive to change. Receiving a visit was seen as a passive activity, while changing prescription habits would require an active behavior that needs to face several barriers and constraints. Detailers agreed with physicians regarding that prescribing changes would also depend on the acceptance of patients and other physicians (mainly hospital specialists).

In the physician survey, 87% replied that visits led to some discussions about the guidelines with their colleagues in the family health unit, 91% mentioned discussing treatment changes with their patients, and 96% agreed that visits had led to prescribing changes in some of their patients

Continuity

In the focus group detailers noted that many physicians told them they enjoyed participating in the visits and wished they could continue. Being able to learn a guideline in a visit was valued as a solution to the lack of time physicians had to study the guidelines by themselves. Even physicians who had previously studied or discussed one or more of the guidelines found visits useful. Some physicians asked if they could receive visits on other guidelines.

This view was shared by the physicians in the questionnaire, 98% agreed that visits were useful to their practice; 95% agreed guidelines were easier to under-

stand in a visit than by reading them; 96% would like visits to continue with other guidelines (mainly on cardiovascular diseases, diabetes and asthma/COPD); and 96% would recommend participating in educational visits to other physicians. As for future visits, 93% considered that educational outreach should be publicly funded by the Ministry of Health; 79% agreed that visits should be carried out by organizations independent of the Ministry of Health; and 80% disagreed they should be limited to primary care units with specific needs.

Discussion

This process evaluation study aimed to analyze the implementation of an educational outreach intervention to change prescribing behavior in primary care and gather participant views. Table 3 summarizes the main recommendations we would make to authors of future educational outreach trials or programs.

Reach

Data shows that recruitment of primary care units took almost 10 months, about twice as long as hoped by the investigators. This may be explained partially by the recruitment strategy. Not having the resources to directly visit more than 200 units, we contacted health center groups and promoted the trial during unit coordinators meetings, expecting them to invite physicians in their units to participate

Table 3 - Recommendations for future trials of educational outreach

- Plan strategies to recruit less motivated physicians.
- Recruit and train a higher number of detailers than needed.
- When recruiting detailers, consider physicians appear to be less receptive to visits made by non-physicians.
- Emphasize persuasion and sales techniques during detailer training.
- Start the intervention as soon as possible after detailers have been trained.
- Involve practice secretaries to improve access to physicians.
- Use text-messages and email reminders to physicians to improve visit success rate.
- Provide physicians with facilitators of patient change, such as patient handouts.
- Ask physicians to indicate their preference to receive individual or small group visits.
- Take delays into account when scheduling visits and provide detailers with indications on how long to wait for physicians.
- Target visits to 15 minutes, but prepare detailers to make shorter and longer visits.

(with the help of brochures prepared by the research team). A motivated unit coordinator was therefore needed to recruit physicians. This probably resulted in the recruitment being more successful among family health units (the newer organizational model of primary care in Portugal) than in the traditional personalized care units and among physicians who were already prescribing aligned with guideline recommendations (motivation to participate in the trial may have been associated with motivation to follow guidelines). Therefore, our sample may not be representative of all primary care units and family physicians in Portugal (where roughly 50% of physicians work in traditional units). Detailer views and physicians answers to the survey show most physicians mentioned they were already following guidelines. However, physicians might perceive their adherence to guidelines as better than it really is,[11] and differences in outcomes between participating units and the regional average in data collected before randomization were small and only significant for COX-2 inhibitors. Recruiting physicians who are more compliant with guidelines may lead to an underestimation of the intervention effectiveness, as physicians who have prescribing habits further away from guideline recommendations (i.e., with the largest room for improvement) may not have been included. Nonetheless, educational outreach programs still depend on physician's willingness to participate. Finding ways to entice the enrollment of less motivated physicians is a challenge that should be addressed in future programs.

This trial showed a high attrition rate among invited detailers, with only half of those who initiated training actually completing visits. This does not hinder the trial's internal validity, but should be considered when recruiting detailers for future interventions. To prevent attrition, we believe starting the intervention as soon as possible after training would be useful. Also, a higher number of detailers than those needed should be trained.

Dose

Visit success rate among participating physicians was high, with almost 90% of visits accomplished and only one physician declining further visits. The dose of the intervention was thus delivered according to plan. Detailers suggested changes that could in the future increase the number of accomplished visits by minimizing the number of times where physicians were unavailable or absent: involving practice secretaries in the program to improve access to physicians and sending text-message or email reminders to physicians a few days prior to the visit.

Each detailer had an average of 13 physicians to visit, about two primary care units. This was enough to accomplish the planned visits even though detailers were also working as full time physicians, with only four of 360 visits being missed because the detailer was unavailable. It also allowed almost 90% of physicians to receive all three visits by the same detailer, with whom they built a working relationship during the trial.

Fidelity

Fidelity of the intervention was very high. A significant effort was made to insure consistency among detailers by training them and providing a common visit script. The full educational content was delivered in 98% of visits and all planned stages were performed by detailers in almost 90% of visits. Three quarters of visits had the planned duration, with the rest being equally divided between shorter and longer visits. In accordance with their training, detailers focused on guidelines key messages when physicians mentioned having little time, and answered questions in detail when physicians showed interest and availability for longer visits.

Detailers were more comfortable delivering scientific information than asking for a prescribing change commitment from physicians and complained about not having received enough training to perform this particular task. Future programs should include greater emphasis on persuasion and sales techniques, recruiting people with adequate expertise in this area to train detailers.

Only a few protocol deviations were recorded during the trial, and most relating to the order of visits. Randomizing the order of visits was planned in order to minimize a possible effect of the physician-detailer relationship, which could grow stronger and make latter visits more effective. However, this complicated the delivery of the intervention. The research team attempted to decrease the impact of these errors by regularly checking what visits had been made and acting promptly to minimize the gap in receiving the intervention among physicians in the same cluster, whilst keeping the planned order for visits.

Acceptability

Almost 90% of surveyed physicians mentioned using the National Health Directorate's guidelines as sources of information about prescribing and detailers recorded physicians disagreeing with the guideline as a barrier in only 5% of visits. Therefore the guidelines chosen for the trial seem acceptable to the vast majority of physicians. The most common barriers to change identified by physicians were related to patient resistance, 20% of physicians in the survey considered that patients were unwilling to change their medications. Hence, facilitators of patient change should be emphasized in future visits. Providing physicians with brochures for patients was a possible solution desired by physicians.

Physicians' claims of already following guidelines were noted as a difficulty by detailers and may be considered as an acceptability issue, instead of a reach problem. Physicians may consider they follow guidelines to the extent that is possible to them, and that in some situations change is not possible. Hence, to be effective, interventions would need to focus on external factors. On the other hand, physicians may have difficulty recognizing their prescribing practice could improve, and so difficulty accepting the need to change.[11] In this case combining educational outreach with audit and feedback about their actual prescribing habits would

probably help physicians realize they have room for improvement. Finally, some physicians may use their claim to already follow guidelines as a way to gain social and professional acceptance from the detailer or as a defensive attitude and thus avoid committing to change. This would mean the intervention had failed in those physicians.

Most physicians received detailers alone or with their residents or medical students, but about 10% asked detailers to deliver the visit together with other physicians. Many more physicians in the survey (about one third) mentioned they preferred not to receive individual visits. Detailers reported some physicians to be more engaged when they were not alone and that having two or three physicians present did not seem to impair their ability to carry out the visit as planned. In future programs, asking physicians to indicate their preference to receive individual or small group visits could be considered. This may decrease visit costs, as detailers will need to perform less visits. However, it can complicate scheduling as physicians might not all be available at the same time. The ability to change physician behavior in small groups (two or three) should also be considered. Offering small group visits to physicians who prefer individual visits might decrease effectiveness of the intervention, while forcing physicians who prefer small group visits to receive detailers individually may also hamper behavior change.

Most physicians chose to receive the visits in their offices, although this made it more likely they would be interrupted by office staff. However, detailers considered these interruptions minor and that physicians would be more comfortable there. Physicians were mostly available in the afternoon which may be an important factor to consider when recruiting detailers and planning visits in the future. Physician delays happened in about 30% of visits, therefore, detailers should not schedule consecutive visits too close together, and allow for enough buffer time when visiting more than one primary care unit in the same day or having to return to their own jobs as physicians. Delays should also be taken into account if detailers are payed by the hour instead of per visit. Guidelines on how long to wait should be defined in advance to help detailers decide when to consider a visit unsuccessful. Visit duration was deemed adequate by most physicians, but 16% considered visits had caused some disruption in their schedule. Detailers mentioned not having enough time in only a small proportion of visits. Hence, targeting visits to last 15 minutes seems appropriate, but detailers should be prepared to deliver only key-messages in 5 minutes or to stay and answer questions in 25 minutes.

Using brochures and physician handouts were considered adequate and useful by most physicians.

Detailers were pleased with their participation in the trial. Intrinsic motivational factors related with improving their knowledge and feeling useful to other physicians were seen by detailers as more important than payment. Detailers wished they could continue this activity, but not if it required them to stop practicing as

physicians, therefore if, as in this case, the chosen detailers are physicians then using part-time detailers would be more appropriate for future visits.

Physicians were largely satisfied with the detailers' performance, considering they showed good knowledge about guideline and good communication skills. However, almost 20% of physicians considered detailers to be more concerned with economic savings than clinical benefits. This is concerning, as physicians who consider that the intervention prioritizes economic savings over patient gains may adhere less to prescribing recommendations.

The vast majority of physicians considered that future educational outreach programs should be publicly funded and most preferred them to be performed by independent organizations.

Perceived impact

Detailers classified the majority of physicians as interested and receptive. However, they perceived visit impact to be small. Overall, physicians indicated they were satisfied with their participation in the trial. The vast majority considered visits were useful, wished they would continue, would recommend them to a colleague, and considered visits had led to some changes in their prescribing behavior. Most physicians mentioned they would not find future visits as useful if made by other health professionals (non-physicians), but would accept family medicine residents. This preference should be considered only as indicative, as physicians in this trial did not actually experience visits by other health professionals.

Study strengths and limitations

Using both qualitative and quantitative methods allowed us to gather a comprehensive view of the intervention implementation. Information gathered in the detailer focus group was essential to understand data entered in the visit tracker, and the survey allowed us to quantify physicians' perceptions and experience complementing data gathered in the interviews. The perceptions of detailers and physicians were very consistent, strengthening our conclusions. This evaluation allows us to raise some hypotheses regarding the mechanisms through which visits work to change behavior. Some of these hypotheses include whether non-physicians are less effective in producing behavior change or if tailoring visits to be conducted individually or in small groups may be considered as a strategy to improve adherence and make physicians more comfortable. These could be tested in future trials.

However, this process evaluation also has important limitations. Detailers observed themselves when they recorded visit information, as we were unable to have independent observers during visits. Yet, having an observer present during the detailer-physician interaction might have interfered with the visit by inhibiting both detailer and physician, as would audio or video recording. The number of detailers in the focus group was small and detailers not attending might have

different views. Nevertheless, other detailers were asked to comment by email and none expressed disagreement. Finally, we did not examine the relation between implementation and outcomes in this study, as outcome data are still being collected. This will be done when outcome data are analyzed.

Conclusions

Implementing an educational outreach program in Portuguese primary care was successful. If a positive change in prescribing habits is shown, then larger and improved educational outreach programs should be implemented. This process evaluation showed that the intervention in the TEP trial was delivered with reasonable reach, high dose and very high fidelity and acceptability. Both physicians and detailers perceived visits to have some impact on prescription behavior, however, this has to be confirmed in the assessment of outcomes. The knowledge gained by this evaluation will help interpret the outcomes of the trial, may guide the further implementation of educational outreach programs and assist other authors when planning similar interventions.

Availability of supporting data

All data regarding prescription is property of the Lisbon Regional Health Administration (Portuguese Ministry of Health). Other researchers wanting to access raw prescription data will need to obtain authorization from this institution before data can be shared. Data regarding the process evaluation is property of the investigators and will be made available upon reasonable request.

Competing interests

The authors declare they have no competing interests and no financial or non-financial conflicts of interest.

Authors' contributions

DP and PAC conceived the study. BH, DSR, IG and IS contributed to planning the process evaluation. DP gathered and analyzed data for the process evaluation and wrote the first draft of the manuscript. All authors contributed to refinement of the manuscript, and approve its final version.

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Manuscript 7: Effectiveness of educational outreach visits compared with usual guideline dissemination to improve family physician prescribing – an 18-month open cluster randomized trial

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Abstract

Background

Educational outreach visits are meant to improve the practice of health professionals by promoting face-to-face visits to deliver educational contents. They have been shown to change prescription behavior, but long-term effects are still uncertain. This trial aimed to determine their effectiveness compared with passive guideline dissemination.

Methods

Parallel, open, superiority, cluster randomized trial. National Health Service primary care practices (clusters) in the Lisbon region – Portugal were recruited and could enter if they had at least four family physicians willing to participate and not planning to retire in the follow-up period. Three national guidelines were chosen for dissemination: acid secretion modifiers, non-steroidal anti-inflammatory drugs and antiplatelets. Physicians in the intervention group received one 15 to 20 minutes educational outreach visit at their workplace for each guideline. Physicians in the control group had access to guidelines through the Directorate-General for Health's website (passive dissemination). Primary outcomes were the proportion of COX-2 inhibitors prescribed within the NSAID class and the proportion of omeprazole within the PPI class at 18 months after the intervention. A cost-benefit analysis was performed. A sample size of 38 primary care practices, with 220 physicians was calculated assuming the intervention would lead to a 5% absolute difference in compliance with guidelines. Practices were randomized by

minimization. Analyses were done at individual physician level using generalized mixed-effects models.

Results

Thirty-eight practices with 239 physicians were randomized. Of 360 planned visits, 322 were successfully delivered. No differences were found between the intervention and control groups regarding the proportion of omeprazole prescribed among IBPs 18 months after the visit (46.28 vs 47.15%, 0.971) or the proportion of COX-2 inhibitors among NSAIDs (12.07 vs 13.08%, p=0.085). All secondary outcomes were also negative. There was no difference in cumulative drug costs at 18 months (3223.50€/1000 patients in the intervention group and 3143.92€/1000 patients in the control group, p=0.848).

Conclusions

Educational outreach visits were unsuccessful in improving compliance with guideline recommendations among Portuguese family physicians. No effects were observed at one, six and eighteen months after the intervention and there were no associated cost savings.

Trial registration

ClinicalTrials.gov number NCT01984034.

Keywords

Educational outreach, Academic detailing, Guideline adherence, Family practice, Drug utilization, Program evaluation, Cost-benefit analysis.

Background

Clinical practice guidelines have the potential to improve the quality of care by summarizing current medical knowledge and promoting interventions with proven efficacy, safety and cost-effectiveness.[1] Yet, issuing guidelines does not guarantee changes in clinical practice, as clinicians may not follow them for a variety of reasons. Among them, not being aware of or familiar with guidelines, considering they are ambiguous or disagreeing with recommendations, perceiving lack of self-efficacy, organizational constraints, and patient barriers.[2,3] This may contribute to the problem of translating new medical knowledge to improvements in public health and of affordability of care.[4,5] To address this problem, several guideline implementation strategies have been tried, with a systematic review finding small to moderate effects in a majority of trials.[6]

Educational outreach visits are a type of strategy aimed at improving clinical practice.[7,8] They consist of face-to-face visits done by an individual (henceforth named a detailer), usually a healthcare professional trained in communication skills, to physicians or other health workers in their own setting. During the visit, the detailer enquires about the physician's baseline knowledge and motivations,

presents content prepared by an independent organization with clear educational goals and using concise and graphic appealing materials, all the while stimulating physician interaction and providing positive reinforcement.[9] Visits are to one individual or a small group, in contrast with large educational meetings. A systematic review concluded that educational outreach visits have a small, but consistent and potentially important, effect on prescription improvement.[8] It also highlighted a gap in knowledge about the performance of this type of intervention in the long term (beyond one year).

Portugal has a public funded National Health Service (NHS) with universal coverage providing the majority of primary care.[10] Primary care services are organized in small local practices, with 4 to 12 family physicians, plus a roughly equal number of nurses and a smaller number of secretaries.[11] Patients are registered with a single family physician, but may visit other physicians within the same practice if theirs is unavailable. Physicians in a practice meet frequently to discuss organization of care and performance indicators (which include items on prescribing). The Directorate-General for Health (an agency of the Ministry of Health) is responsible for issuing prescribing guidelines.[12,13] Guidelines are made available on the agency's website and all health professionals are supposed to abide by them. This makes all physicians in Portugal exposed to the guidelines simultaneously. However, their effectiveness in changing actual practice has not been studied.

In Portugal, family physicians work in group-based practices. Although educational outreach visits are directed at individual physicians, contamination among physicians working in the same practice is a plausible concern. In addition, a public health program of educational outreach visits would probably be delivered to all doctors in the same practice to minimize costs and loss of detailer time traveling. Thus, it may be more reasonable to assess educational outreach visits in the context of Portuguese primary care using a cluster-randomized design.

The primary objectives of the Trial to Assess the Effectiveness of Educational Outreach in Prescription Guidelines (TEP trial) were to determine if educational outreach visits, compared with passive guideline dissemination, resulted in a reduction of the proportion of COX-2 inhibitors prescribed among the NSAID class and an increase in omeprazole prescriptions among the PPI class 18 months after the visit (long-term). Secondary objectives were the effects on the same drugs at 1 (short-term) and 6 months (medium-term), and the short, medium and long-term effects in the prescription of clopidogrel. Thus, the duration or persistence of effect post intervention. The trial also aimed to determine the cost-benefit of educational outreach visits.

Methods

The protocol for this trial has been published previously, along with a PaT plot, and a cascade diagram.[14]

Trial design

The TEP trial aimed to determine the long-term effectiveness of educational outreach visits and their cost-benefit relation. It was a parallel, open, superiority, cluster-randomized controlled trial conducted in Portuguese primary care physicians. Clusters were Portuguese NHS primary care practices.

Participants

The trial recruited family physicians working in NHS practices of the Lisbon region, Portugal. A practice would be eligible to participate if it had at least four physicians. All family physicians were eligible, except those planning to retire or without a stable patient list. Participants were recruited through practice coordinators. Family practices with at least 4 consenting family physicians served as the units of randomization. There was no financial incentive to participation. Participating physicians completed a baseline characteristics questionnaire and consented to schedule educational outreach visits and to the collection of their aggregate prescription data.

Interventions

Three guidelines were chosen for dissemination: non-steroidal anti-inflammatory drugs (NSAID), acid secretion modifiers and proton pump inhibitors (PPI) and antiplatelets.[15-17] Physicians randomized to intervention clusters received three educational outreach visits during a six-month period. Key-messages were identified in each guideline. The NSAID guideline advocated for less use of COX-2 inhibitors, recommending they would only be prescribed to patients with increased gastrointestinal risk who did not tolerate a classical NSAID with a gastroprotective agent. For acid secretion modifiers, the guideline recommended that omeprazole should be preferred as it was as effective as other proton pump inhibitors and less expensive. The antiplatelets guideline recommended less use of clopidogrel, which should not be maintained long term after myocardial infarction, acute coronary syndrome, or percutaneous coronary intervention. Thus, we had a diverse mix of objectives aimed at improving rational prescribing where the objectives in one case where increasing the usage of a specific drug and in two other cases decrease drug usage.

Each visit was planned to focus on one guideline, last 15 to 20 minutes and have one family physician present (up to three were allowed if physicians preferred, but one-to-one visits were encouraged). The visit would begin with an introduction about the detailer and the purpose of the visits, confirming the physician's availability. Then educational needs would be assessed by asking about the physician's

usual practice with open questions. These would shape how the detailer would deliver key-messages about the guideline, addressing scientific evidence, and benefits of following the guideline, barriers and facilitators of change. The physician would be given the opportunity to present objections, which were addressed by the detailer. The visit ended with a summary and encouragement for the physician to commit to change. A point of care summary was distributed with each visit and a brochure was used by the detailer as a visual aid. Copies of the brochures and point of care summaries are made available in appendix 1.

Whenever possible, a single detailer performed all three visits to the same physician. Visits could take place in between patient visits or at other times indicated by the physician. Visits could be rescheduled up to the day before they were planned, but if the physician was unable to attend and could not warn the detailer beforehand that visit would be skipped. Detailers filled a short questionnaire at the end of each visit, included those that were not successful.

The detailers were three members of the research team (two family physicians and one academic pharmacologist) and nine physicians that were trained for the trial (six family physicians and three family medicine residents). All detailers were trained on the principles of educational outreach and the contents of each visit, to ensure consistency.

For the control group, usual guideline implementation consisted of passive dissemination by their publication on the Directorate-General for Health's website.

Outcomes

The trial had two primary outcomes, measured at the physician level: the proportion of COX-2 inhibitors prescribed within the NSAID class and the proportion of omeprazole within the PPI class, both measured in defined daily doses at 18 months after the intervention. There were seven secondary outcomes: the same proportions of COX-2 inhibitors and omeprazole measured at one and six months after the intervention, and the number of defined daily doses of clopidogrel per 1,000 registered patients at one, six and 18 months after the intervention.

We also conducted a cost-benefit analysis using the sum of all prescriptions dispensed for NSAIDs, acid suppressive therapy (PPIs, H2-receptor antagonists, misoprostol and reimbursed anti-acids) and clopidogrel from month one following the intervention until month 18. Costs were considered from the perspective of a government supported program, with government as the payer, therefore only the reimbursed portion of drugs was considered. Differences in costs between the intervention and control group would be compared with the cost of training and paying detailers, preparing and printing educational materials, program coordination and indirect costs of physician time (spent with a detailer rather than seeing a patient).

Only prescriptions that were dispensed were counted. Drug dispensing and cost data was provided by the Lisbon Regional Health Administration. In the Portuguese health system, prescriptions can be made for acute or chronic conditions. The former are valid for dispensing within 30 days and the later for six months. Of the studied drugs, only NSAIDs cannot be prescribed for chronic use. Physicians who transferred to other practices within the health region were followed and their prescriptions monitored. When prescription data was not available, the last known month's prescription was used.

Sample size

Pilot data was obtained from three primary care practices and was used to estimate within unit variability and the intra-cluster correlation coefficient. Aggregate data from the Regional Health Administration was used to estimate the mean prescription and standard deviation for primary outcomes. Our sample size was calculated assuming the intervention would lead to a 5% absolute difference in compliance with guidelines between intervention and control units for primary outcomes, a mean cluster size of six physicians per practice, a 1:1 allocation ratio of controls per intervention unit, an alpha type error of 0.025, and a dropout rate of about 15%. To achieve 80% power, a sample of 110 physicians in each group was needed. To recruit the necessary 220 physicians, 38 primary care units would be required. STATA 12.0 (STATA Corp, TX, USA) and its sampsi and sampclus commands were used to calculate sample size.

Randomization

Clusters were allocated to the intervention or control groups using minimization, a method to achieve good balance regarding baseline characteristics that could influence the outcomes when the number of clusters is small.[18] We stratified for number of physicians in a practice, median baseline prescription of COX-2 inhibitors and omeprazole (above or below the regional median), proportion of physicians with fewer than 10 years of practice after completing vocational training, and type of primary care practice. The sequence of intervention visits for each practice was determined by simple randomization using Random.org sequence generator.[19]

Allocation was concealed by having the project manager assign a sequential number to each practice as it completed enrollment. The trial statistician received only anonymized data (sequential number and minimization variables), blindly allocated practices to each trial arm and returned allocation information to the trial manager.

Neither participating physicians nor detailers could be blinded. Outcomes were collected independently from the researchers by the Regional Health Administration and were only provided after the intervention had ended. Unlike what was planned in the protocol, the lead author could not be blinded to group and

visit sequence allocation because the Regional Health Administration needed to consult with study author for data extraction. However, we were able to keep the trial statistician blinded.

Statistical methods

Analysis was performed using the intention to treat principle. Physicians who transferred to another unit in the region were followed and for those we were unable to retrieve prescription data we used the last working month's prescription. Outcomes in both groups were compared using generalized mixed-effects models. For model calculations, proportions of omeprazole and COX-2 inhibitors were logarithmically transformed [$x = \ln(x/(1-x))$] because of non-normal distributions. Intra-cluster correlation coefficients were calculated for primary outcomes. Statistical significance was assumed for a p-value less than 0.025. STATA 12.0 (STATA Corp, TX, USA) was used to conduct the analysis. No interim analyses were done. We conducted three post-hoc sensitivity analyses: excluding physicians with missing data on the month of the outcome, including only physicians with no more than two months missing data in the post-intervention period, and adjusting for the physician's observed baseline prescription.

Given the intervention posed minimal risks to patients, no data monitoring committee was established and no stopping guidelines were defined.

Ethical approval

The trial was approved by the ethics committees of the Lisbon Regional Health Administration and NOVA Medical School. Family physicians invited to participate received written information about the main aspects of the trial and participants gave consent for researchers to access their prescription data. The trial only collected aggregated and non-identifiable patient data.

Results

Participants

Recruitment began in March 2013 and ended in January 2014. Participant flow is shown in figure 1. The research team met with practice coordinators from 13 of 15 health center groups in the Lisbon Region, representing 233 practices. Of these, 193 did not reply to subsequent contacts, were unwilling to participate or self-excluded for having less than four physicians willing to participate. Two units had shown interest in participating, but were excluded when other units completed enrollment first. We randomized 38 clusters with 239 participating physicians.

Baseline characteristics for participants in the intervention and control groups are shown in table 1. Groups were balanced regarding the characteristics used for minimization. However, the number of patients per physician was higher for the intervention group.

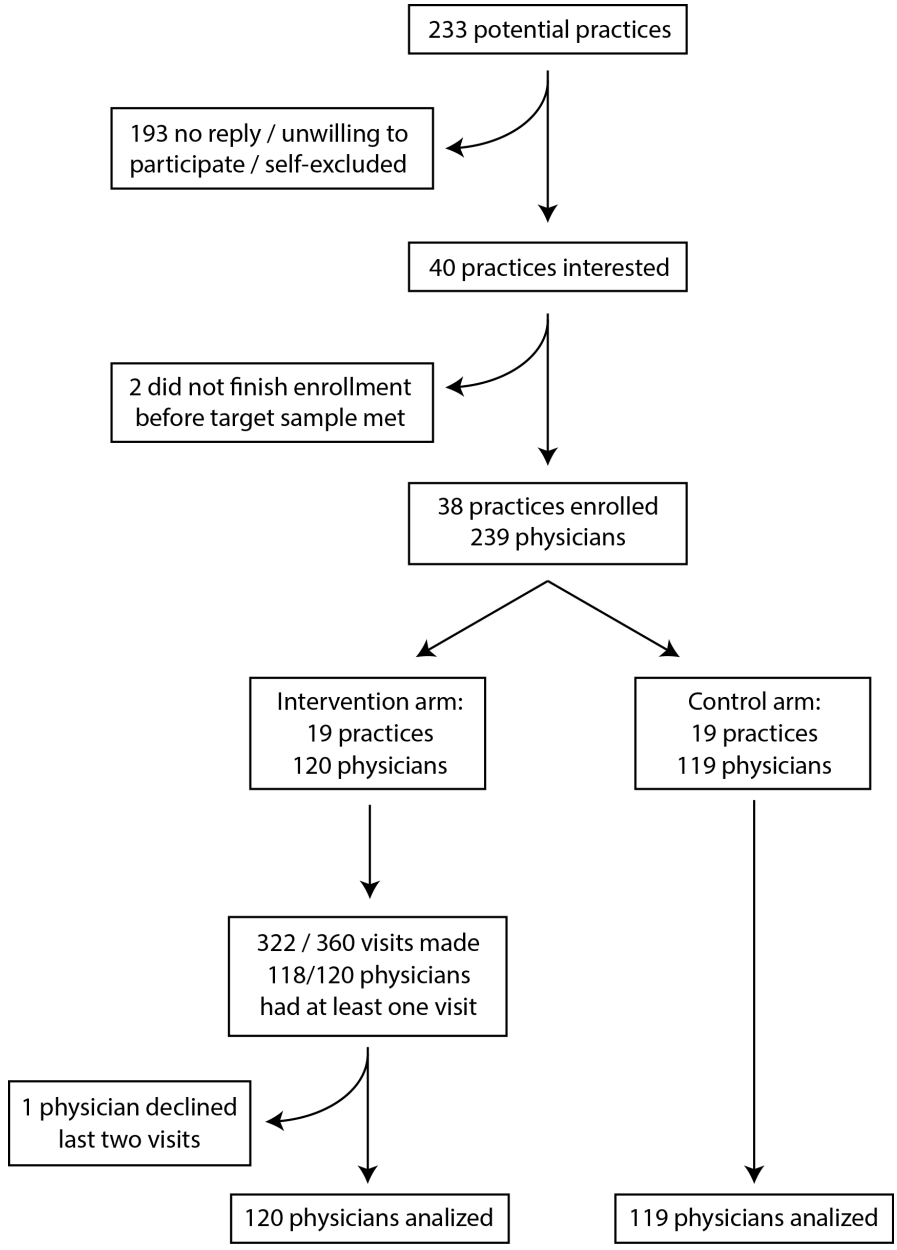

Figure 1 – Participant flow diagram.

Delivery of the intervention

Of the 360 planned visits, 322 (89.4%) were successful. Another twenty-six visits were attempted but failed because the physician was absent (21) or unavailable (5). One physician declined the last two visits after the first failed, but did not withdraw consent to participate in the prescription analysis. Two physicians had

Table 1 – Baseline characteristics of participating physicians.

	Intervention	Control
Physicians per cluster – mean (standard deviation)	6.3 (1.4)	6.3 (1.4)
Unit type – n units (n physicians)		
Family health unit	17 (107)	18 (114)
Personalized care unit	2 (13)	1 (5)
Female – %	70.8	79.0
Age – years, median (P25-P75)	52 (41-59)	47 (38-59)
Years in practice – median (P25-P75)	13 (6.5-28)	11 (4-28)
Residency tutor–- %	55.8	52.9
Patient list size – median (P25-P75)	1874 (1812-1923)	1813 (1746-1872)
Prescription – mean (standard deviation)		
Omeprazole, %	47.13 (13.50)	48.30 (13.70)
COX-2 inhibitors, %	13.20 (9.69)	14.67 (12.88)
Clopidogrel, DDD/1,000 patients	0.0986 (0.0502)	0.1053 (0.0491)
NHS expenditure with NSAIDs, acid secretion modifiers and clopidogrel / month / 1,000 – €, mean (standard deviation)	189.60 (73.41)	192.72 (85.67)

COX-2 – cycloxigenase-2. NHS – National Health Service. NSAIDs – non-steroidal anti-inflammatory drugs.

none of the planned visits (6) as they were on extended leave. Two visits were not done because physicians were on short leaves. Finally, two visits failed because the detailer was unavailable. Only the target physician was present in 89.1% of successful visits. The three visits were all made by the same detailer in 88.3% of physicians. Detailers reported delivering the full educational content in 97.8% of visits.

Follow-up

Prescription data was available for both primary outcomes in 116 of 120 physicians in the intervention group and for PPIs in 112 and for NSAIDs in 108 of 119 physicians in the control group. Secondary short-term outcomes (1 month after the intervention) were available for 98.3% and 99.2% of the control and intervention groups, respectively; and medium term (6 months after the intervention) for 96.9 and 97.6%. Overall, 29 physicians had one or more months without prescription data for one of the studied drugs (16 in the control group and 13 in the intervention group). Three physicians in the control group and two in the

intervention group had no prescriptions of any of the studied drugs in the final six months of the study. For the remaining physicians, there were prescriptions after one or more months without data, suggesting temporary absences and not losses to follow-up.

Intervention effects

The results of the intervention are shown in table 2 and figure 2. There were no differences between the intervention and control groups regarding primary outcomes: proportion of omeprazole among IBPs and proportion of COX-2 inhibitors among NSAIDs at 18 months after the intervention. The intra-cluster correlation coefficient was 0.305 (95% confidence interval 0.177-0.473) for omeprazole prescriptions at 18 months. No significant inter-cluster correlation existed for COX-2 inhibitors at 18 months. There were also no significant differences in secondary outcomes, in total costs or class-specific costs for the period between 1 and 18 months after the intervention.

Table 2 – Prescription and cost of the studied drugs at 1, 6 and 18 months after the intervention.

	Intervention (n=120)	Control (n=119)	p
Omeprazole, % (95%CI)			
+1 month	46.86 (44.34-49.39)	47.36 (44.81-49.91)	0.744
+6 months	48.02 (45.58-50.46)	47.90 (45.01-50.79)	0.696
+18 months (*primary*)	46.28 (43.77-48.79)	47.15 (44.39-49.91)	0.971
COX-2 inhibitors, % (95%CI)			
+1 month	11.70 (9.83-13.57)	15.38 (12.87-17.90)	0.131
+6 months	11.59 (9.28-13.89)	15.74 (13.42-18.05)	0.061
+18 months (*primary*)	12.07 (9.75-14.41)	13.08 (10.75-15.41)	0.085
Clopidogrel, DDD/1000 (95%CI)			
+1 month	0.098 (0.886-0.107)	0.103 (0.094-0.112)	0.456
+6 months	0.090 (0.082-0.098)	0.099 (0.089-0.108)	0.230
+18 months	0.091 (0.083-0.100)	0.091 (0.082-0.100)	0.840
Cost 1-18m / 1,000, € (95%CI)			
Gastric secretion modifiers	1647.79 (1541.37-1754.21)	1626.38 (1511.76-1741.01)	0.880
NSAIDs	1099.26 (984.70-1213.81)	983.02 (873.49-1092.55)	0.515
Clopidogrel	476.45 (428.34-524.57)	539.05 (491.22-586.87)	0.184
Total	3223.50 (2999.55-3447.44)	3143.92 (2917.61-3370.23)	0.848

CI – confidence interval

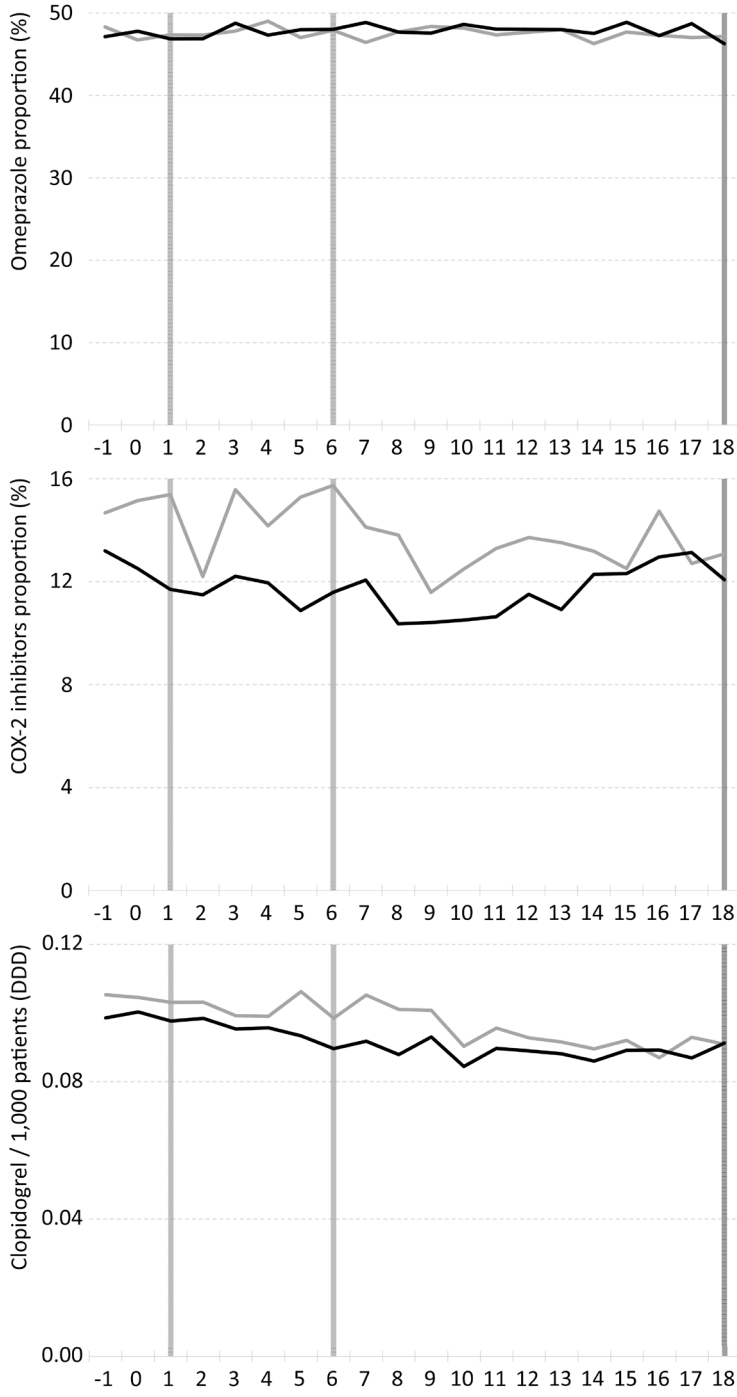

Figure 2 – Prescription timeline of drugs in primary and secondary outcomes (vertical bars) from one month before the intervention (-1) to 18 months after the intervention (18) in the intervention (black line) and control (grey line) groups.

Differences between groups remained non-significant when we did three separate sensitivity analyses excluding physicians with missing data on the month of the outcome, including only physicians with no more than two months missing data in the post-intervention period and when we adjusted for the physician's observed baseline prescription.

As there were no differences in costs between groups, we did not perform a formal cost-benefit analysis.

Discussion

Summary of main results

Our results showed no effect of an intervention consisting of educational outreach visits to modify prescribing of family physicians to align with national guideline recommendations. Neither short, medium nor long-term effects were seen and no differences in drug costs were found between the intervention and control groups.

Strengths and limitations

The planned intervention was adequately implemented: educational visits were delivered with a very high success rate, were accepted by the clear majority of participants and had the planned educational content. The intervention was similar to what would have been a government funded educational outreach program. Outcome data was collected independently of the researchers from and administrative database, hence we had few missing data points. We hypothesize that missing data points correspond to absence from work due to illness, maternity or paternity leave or other unforeseen causes, and that it is likely that data is missing completely at random and not related with being assigned to the intervention or control groups. We could gather long-term follow-up data for most physicians, which allowed the study of the intervention's effects over time. Only five among 239 physicians had no data points for outcomes in the last six months and may have been lost to follow-up (although we cannot be certain these were not temporary interruptions). Costs were measured along site the effects on drug use, considering the whole pharmacological class and not just one drug (as costs could have been transferred between drugs within a class). Having the order of visits randomized between clusters allowed us to exclude effects of a possible build-up of the detailer-physician relation. Finally, results are consistent across the different drug classes studied.

The major limitation for the trial is that there was likely selection bias for participation. When compared with regional data, recruitment was higher among family health units than among personalized health care units, the observed baseline proportion of COX-2 inhibitors was lower than in our pilot data for the region, as was the baseline proportion of omeprazole.[14] Although randomization was able

to balance the groups regarding characteristics selected for minimization, there was some imbalance regarding patient list size. This certainly influenced absolute costs, and is why we present costs per 1,000 registered patients. It is uncertain if it could have influenced prescriptions, as baseline levels for the drugs of interest are similar (the intervention group was slightly worse in omeprazole prescriptions and better in COX-2 inhibitors and clopidogrel prescriptions). Another limitation was known from the outset and relates to prescription data. We used prescriptions that had been dispensed at a community pharmacy and not all prescriptions issued by the participating physicians. This was because information on issued prescriptions is less reliable in the database and our pilot data showed a large percentage of prescribed drugs were never actually dispensed (due to factors like lack of patient adherence, mismatch between the patient's needs and the number of prescribed packages, loss of prescriptions, and errors when issuing the prescription).[14] Dispensing can occur up to 30 days after a prescription is issued for NSAIDs and up to six months for PPIs and clopidogrel. Hence, part of the prescriptions dispensed for PPIs and clopidogrel had not been issued in the same or the previous month.

Another issue to consider is the relatively large random monthly variation in prescription outcomes, which suggests our sample size may have been small to handle physicians with low prescription volume. Considering our choice of when to measure short, medium and long-term outcomes is somewhat arbitrary, this may have been an issue when measuring short and medium-term outcomes, where this fluctuation is more apparent for COX-2 inhibitors and clopidogrel.

Interpretation of the results

A meta-analysis of educational outreach visits showed a median adjusted risk difference in compliance with a desired prescribing practice of 4.8%, concluding educational outreach visits had an effect on prescribing.[8] Our study aimed to contribute one of the unanswered questions in this meta-analysis: if visit performance deteriorates in the long-term. However, we were unable to find any short, medium or long-term benefits of educational outreach visits. One possible reason for lack of effect is that physicians more interested in improving their prescribing behavior self-selected for the trial and baseline prescription was already more compliant with guidelines than in physicians who did not volunteer to participate. It is possible that we did not target what Soumerai describes as "high-potential" physicians – those with prescribing patterns more distant from guideline recommendations, hence, more potential to change.[9,20] Given the control group was also exposed to the same guidelines, it is also possible the intervention was not so effective when used as an add-on to existing dissemination strategies. The Portuguese context may have been important regarding the effects of the intervention, as primary care physicians are government employed, their performance

is monitored through quality and spending indicators, and the National Health Directorate's position on guidelines is that they are normative in nature.[10]

Not having shown an effect in short and medium-term outcomes limits our ability to conclude on the long-term effects of educational outreach visits. Even though there was no statistical significance, we could observe some separation between groups in NSAIDs between two and five months after the intervention and in clopidogrel between five and eight months, both favoring the intervention group. A larger delay for clopidogrel is consistent with the fact that its prescriptions are valid for six months. However, even these small differences seem to disappear by the end of the follow-up period. This suggests that, even if we had found positive results in the short and medium-term, effects would deteriorate over time.

Costs throughout the follow-up period were not significantly reduced in the intervention group, making any investment we did in producing educational materials, training detailers and conducting the visits ineffective.

Conclusions

Educational outreach visits were unsuccessful in improving Portuguese family physicians' compliance with guideline recommendations to decrease the relative use of COX-2 inhibitors in NSAID prescriptions, increase the relative use of omeprazole in PPI prescriptions and decrease clopidogrel use in antiplatelet prescriptions. No effects were observed at one, six and eighteen months after the intervention and there were no associated cost savings.

Ethics approval and consent to participate

The trial was approved by the ethics committees of the Lisbon Regional Health Administration and NOVA Medical School. Family physicians gave consent to participate. The trial only collected aggregated and non-identifiable patient data.

Availability of data and materials

The data that support the findings of this study is property of the Lisbon Regional Health Administration (Portuguese Ministry of Health), and restrictions apply to its availability. Data was used with authorization for the current study. Data is however available from the authors upon reasonable request and with permission of the Lisbon Regional Health Administration.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DP and PAC conceived the study. ALP, BH, DSR and IS contributed the study design. ALP, DP, DSR and PAC calculated sample size and planed the statistical analysis. PAC was the grant holder. DP, DSR, IG, IS and PAC contributed to recruitment of participants, training of detailers and preparing educational content. DP, DSR and PAC acted as detailers. IG was the trial manager. DP worked with the Regional Health Administration to collect data. DP and ALP conducted the statistical analysis of results. All authors contributed to drafting the manuscript, reviewed its content and approve of the final manuscript.

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Part VI - Conclusions

Global interpretation

Influences on family physicians to prescribe

The two studies in the Portuguese Sentinel Practice Network had similar findings in most respects. Portuguese physicians are treating hypertension and diabetes mostly in accordance with current guidelines for these conditions. They mainly use angiotensin converting enzyme inhibitors, thiazide and thiazide-like diuretics and angiotensin receptor blockers to treat hypertension, and metformin to treat type 2 diabetes. In both cases, family physicians make most diagnosis and are responsible for deciding treatment. When patients have seen other physicians first and already started treatment, it will rarely be changed by the family physician.

It is concerning that, although patients seem to initiate recommended treatments, the observed prevalent pattern of drug use in hypertension and type 2 diabetes in Portugal deviates from national and international recommendations. Sometime after the initial diagnosis and treatment decision the prescribed drugs will change to less cost-effective options.

There were not many differences between family physicians and hospital or private practice based specialists regarding the choice of the most common anti-hypertensives, but there were large differences in the decision to initiate pharmacological treatment in diabetes and which agents were chosen: specialists were more likely to use the newer DPP-4 inhibitors. These findings suggest that, at least for type 2 diabetes, specialists may have an important role adopting a newer and more expensive drug class and this probably influences family physicians prescribing, as they rarely changed the initial treatment.

One hypothesis to explain this difference between hypertension and diabetes is that the novelty of drugs may be an important factor. DPP-4 inhibitors are still relatively new drugs and under patent protection in the Portuguese market. While in hypertension only aliskiren and some fixed-dose associations are still under patent protection, none of which are frequently used as first-line therapy. If this is true, then similar differences between family physicians and other specialists could have existed in anti-hypertensives like ACE inhibitors and angiotensin receptor blockers when they were first introduced, but then faded over time.

Impact of regulatory authorities' recommendations

Regulatory interventions on trimetazidine and nimesulide resulted in significant declines in the use of these drugs. For trimetazidine, there were few concurrent interventions that could explain the observed changes in prescribing, and it is very probable that the association between regulatory intervention and decreased use was causal. For nimesulide there were many other factors concurring with regulatory interventions, making it difficult to assess the importance of each individually. For trimetazidine, when European authorities announced a safety review

there was no change in use, while for nimesulide this announcement coincided with a sudden decrease in dispensing. It is probable that, when a drug's adverse events are reported by media, doctors, patients and pharmacists become more aware of recommendations and change their behavior, even if no regulatory decision exists. Of note, nimesulide would not have been reported in media if the European Medicines Agency hadn't decided to initiate a safety review. Therefore, one can consider that media reports stem from actions taken by regulatory agencies. Yet, not all recommendations will be picked up by general media, and effects on drug use should be studied with and without media reports.

In either drug, several years after safety measures were implemented, use tends towards stabilization at a lower level than before the intervention. Use of trimetazidine and nimesulide did no disappear, and two possibilities arise: either most physicians are using it less frequently and in patients that meet new criteria for use, or at least some physicians keep using the drugs despite the recommended restrictions.

Both studies point to the existence of differences in response to regulatory measures between family physicians, hospital clinicians and doctors in other sectors of the health system. Family physicians seem to be more compliant with recommendations for restricted use. These differences weren't large, but they may indicate the need to address context and individual characteristics of physicians to improve the efficacy of safety measures.

Importantly, we could not find a decrease in clinical adverse events in the nimesulide study. Two explanations are plausible: that there was an increase in reporting associated with greater awareness of the drugs side effects, or that restrictions were ineffective in changing clinical outcomes.

Educational outreach visits to influence prescribing behavior

Our trial did not show a change in prescriber behavior with educational outreach visits. A negative result for educational outreach visits is contrary to the majority of literature in this field, but by no means unique. We believe that the study was adequately designed and the intervention was well implemented, as shown in our process evaluation study. Most physicians found the visits useful, wished the visits would continue and would recommend the program to other physicians, although there were no actual changes in prescribing behavior. This suggests that it is unlikely the negative result was a consequence of a poorly implemented intervention or one that was unacceptable to physicians.

There are probably two major factors that contributed to this result: selection of participants and context. Physicians participating in the trial were voluntary participants, and it is likely that those more motivated to be cost-effective prescribers were the ones who volunteered. This idea is supported by the low recruitment rate of personalized care units (the traditional primary care organization in Portugal)

compared with family health units (the reformed primary care), and lower use of COX-2 inhibitors. Also, when comparing data from the nimesulide study, physicians in our sample prescribed this drug less often than the national average for primary care. They did, however, use less omeprazole than the regional average in our pilot data. But there was a significant interval between collecting pilot data and initiating the trial, during which omeprazole use compared to other PPIs may have declined (due to changes in relative costs of different PPIs or because of the introduction of generic esomeprazole). It is possible that physicians in the study were already among the best prescribers and therefore had little margin to change. Targeting physicians with prescribing patterns less compliant with guidelines could have led to different results. However, physicians cannot be forced to participate in a randomized trial or receive educational visits. The need for physicians to accept the intervention is probably one of the limitations of educational outreach visits as a tool to change behavior.

Context factors are also important. The intervention may have failed because of specific factors in Portuguese primary care. The Directorate-General of Health's guidelines are actually named "norms" in Portuguese, and they are viewed as normative in nature by this body and by some physicians. This may result in physicians highly aware of and familiar with guidelines, and motivated to comply, because they feel obliged to or because of other factors like performance indicators used to determine financial incentives for physicians. Our premise that publishing guidelines on the Directorate-General of Health would not lead to behavior change might have been untrue, making the additional dissemination with educational outreach visits unnecessary.

Given our negative results at short and medium term, results relative to the long-term impact of educational outreach visits must be interpreted with caution. The variation observed favors deterioration and not improvement of the effect over time.

Our data will hopefully contribute to an update of the systematic review on educational outreach visits and our process evaluation will help interpret the observed results.

Implications for practice

When assessing family physicians' prescribing choices, it will be important to determine the extent to which other prescribers are an important influence. Prescribing guideline compliance should preferably be done alongside the introduction of new drugs, and hospital and private practice based physicians should also be monitored. Although family physicians are responsible for most diagnosis and new prescriptions, efforts to improve quality should be directed at groups that have larger deviations from desired practice.

Actions taken by regulatory agencies are likely to have an effect in drug use, although concurrent factors may also play an important role and should be considered or even taken advantage of to increase efficacy. The use of a drug under intervention does not disappear and adverse events may still occur. There can be differences in the uptake of recommendations by different groups of doctors and interventions may need to be customized to specific targets.

Generalized implementation of educational outreach visits in Portuguese primary care as a strategy to increase compliance with national guidelines should not be done. Targeting physicians least compliant with guidelines might be effective, but this requires further research.

Implications for future research

It will be important to clarify the extent to which family physicians are different from other physicians when a new drug is made available. Prescription changes in prevalent cases should be studied to determine how initial therapy changes as time from diagnosis passes, namely which drugs or classes are removed or introduced, the reasons for change and who are the physicians responsible for those decisions. Cohort studies would be appropriate designs to monitor such changes, as they allow for interaction with patients and physicians over time. Studies in reimbursement databases are also possible and may be less expensive. However, researchers should first guarantee that administrative information is valid and complete, and confidentiality issues when extracting individual patient or physician data need to be taken under consideration.

Determining the impact of regulatory measures needs further study. It is not feasible to conduct a randomized controlled trial, as there is no control group of unexposed physicians and patients (postponing safety measures would be unethical, and, for positive measures like new indications, contamination would be very likely to occur). This makes quasi-experimental designs like the interrupted time-series the best tool available. However, interrupted time-series cannot separate events that occur simultaneously or very close to one another. For these, evidence needs to be accumulated from several studies (using different drugs and in distinct settings) for a pattern to emerge on which interventions or components are most effective. Another subject that merits research is analyzing differences between physicians or groups of physicians. It seems likely that average responses measuring aggregate data conceal variable efficacy among different populations of physicians or patients. Learning if these differences are real and understanding why they occur could help tailor future interventions to maximize their effect. Finally, clinical outcomes must be a part of evaluating the impact of regulatory measures whenever possible, as intentions do not always translate into actual results that mater to patient safety.

The results of our trial in educational outreach visits should be further analyzed to help understand why the intervention failed. This kind of post-hoc investigation has many limitations, but may generate hypothesis that can be tested in the future. We plan to analyze subgroups of physicians, testing the interaction between basal compliance with guidelines, the type of practice, physician characteristics and replies to our post-intervention survey and observed prescribing. Testing if different detailers, how visits were delivered and if the order of visits were important is also planned. Future studies should keep addressing the long-term effects of educational outreach visits to confirm if they deteriorate over time.

Final remarks

Understanding doctors' prescription behavior is not simple. Human behavior is complex, dependent on individual and contextual factors, with many interactions, changes over time and circumstances may lead to different responses. Unlike studying diseases and drugs, one cannot explain physician behavior with a physiological mechanism. Trying to change a physician's behavior adds complexity, as one can't prescribe X milligrams of an intervention like educational outreach visits or isolate the intervention from its context. Aiming to help doctors make better decisions for patients by choosing more effective, safer and more cost-effective drugs remains a worthy goal, but there is no easy or one size fits all solution that can be easily deployed.

A global result of this thesis is that the Family Medicine Unit at NOVA Medical School now has experience in analyzing large prescription databases in the Portuguese National Health Service, organizing and conducting a randomized controlled trial and a process evaluation, as well as knowledge on some advanced statistical techniques (segmented regression models, hierarchical models, and randomization by minimization). These could benefit future research projects and post-graduate students.